Rs.10

JIMA

Volume 67 (RNI) ♦ Number 10 ♦ OCTOBER 2023 ♦ KOLKATA

JOURNAL *of the* INDIAN MEDICAL ASSOCIATION

Official Publication of the Indian Medical Association

Indexed in

INDEX COPERNICUS INTERNATIONAL

Scopus®

Volume 121 (JIMA) ♦ Number 10 ♦ October 2023 ♦ KOLKATA

Dr ©

Largest Circulated Medical Journal in India

ISSN 0019-5847

94 TH YEAR OF PUBLICATION

Visit us at https://onlinejima.com

TEAM IMA (2022-24)


Chief Patron
Past President,WMA,MCI, IMA
Dr Ketan Desai


National President
(2022-23)
Dr Sharad Kumar Agarwal


Imm. Past National President
(2022-23)
Dr Sahajanand Prasad Singh


National President
(2023-24)
Dr R.V. Asokan


Hony. Secretary General
(2022-24)
Dr Anilkumar J Nayak


National Vice President
(2022-23)
Dr. Jayesh M Lele


National Vice President
(2022-23)
Dr Sachchidanand Kumar


National Vice President
(2022-23)
Dr Shailesh H Shah


National Vice President
(2022-23)
Dr Daggumati Shree Harirao


National Vice President
(2023-24)
Dr R Gunasekaran


National Vice President
(2023-24)
Dr. Suresh Gutta


National Vice President
(2023-24)
Dr Ashok Sharda


National Vice President
(2023-24)
Dr Shiv Kumar Utture


Hony. Finance Secretary
(2022-24)
Dr Shitij Bali


Hony. Joint Secretary
from NCR (2022-24)
Dr Munish Prabhakar


Hony. Joint Secretary
from National Capital
Region (2022-24)
Dr. Prakash Lalchandani


Hony. Joint Secretary
from rest of the country
(2022-24)
Dr. M. Venkatachalapathy


Hony. Joint Secretary
stationed at Calcutta
(2022-24)
Dr. Pradeep Kumar Nemani


Hony. Joint Secretary
nominated by National
President (2022-23)
Dr Anand Prakash


Hony.Jt Finance Secretary
from rest of the country
(2022-24)
Dr Mahendra Nath Thareja


Hony. Joint Finance Secretary
stationed at Calcutta
(2022-24)
Dr Sarbari Dutta

IMA College of General Practitioners


Hony. Asstt. Secretary
from NCR (2022-24)
Dr Thakur Padmanabhan


Hony. Asst. Secretary from
rest of the country (2022-24)
Dr Paramjit Singh Maan


Dean, IMA-CGP
(2022-23)
Dr Rayapu Ramesh Babu


Dean, IMA-CGP
(2023-24)
Dr Satyajit Borah


Vice Dean,IMA CGP
(2022-24)
Dr Poonam Singh


Hony. Secretary
IMA CGP (2022-24)
Dr. R Anburajan


Hony. Joint Secretary IMA CGP
from Tamilnadu (2022-24)
Dr M Thiraviam Mohan


Hony.Jt.Secy.,IMA CGP
from Tamilnadu (2022-24)
Dr D Senthil Kumar


Hony. Joint. Secy. IMA CGP from
rest of the country (2022-24)
Dr Satish joshi


Hony. Joint. Secy. IMA CGP from
rest of the country (2022-24)
Dr Sunil Bhikhabhai Chenwala


Hony. Joint. Secy.,\, IMA CGP
from rest of the country (2022-24)
Dr Yeshwant Vasantrao Gade


Hony.Joint.Secy. IMA CGP from
rest of the country (2022-24)
Dr Pavankumar N Patil

TEAM IMA (2022-24)

Journal of IMA


Hony. Editor-JIMA
(2022-23)
Dr Nandini Chatterjee


Hony. Editor-JIMA
(2023-24)
Dr Sanjoy Banerjee

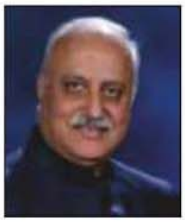

Hony. Associate Editor
JIMA (2022-24)
Dr Ranjan Bhattacharyya


Hony. Associate Editor
JIMA (2022-24)
Dr Prasanta Kr. Bhattacharyya


Hony. Secretary
JIMA (2022-24)
Dr Sibabrata Banerjee


Hony. Asstt. Secretary
JIMA (2022-24)
Dr Meenakshi Ganguly

IMA Academy of Medical Specialities


Chairman, IMA AMS
(2022-23)
Dr Pankaj Mutneja


Chairman, IMA AMS
(2023-24)
Dr Nomeeta Shiv Gupta


Vice Chairman, IMA-AMS
(2022-24)
Dr Nibedita Pani


Hony. Secretary, IMA-AMS
(2022-24)
Dr Srirang Abkari

IMA AKN Sinha Institute


Director
IMA-AKNSI (2022-23)
Dr G N Prabhakara


Director
IMA-AKNSI (2023-24)
Dr Ramneek Singh Bedi


Hony. Executive Secretary
IMA-AKNSI (2022-24)
Dr Sanjiv Ranjan Kr. Singh


Hony. Joint Secretary
IMA-AKNSI (2022-24)
Dr Deepak Kr. Singh


Hony. Joint Secretary
IMA-AKNSI (2022-24)
Dr Parul Vedgama

Your Health of IMA


Hony. Editor
Your Health (2022-24)
Dr Kakoli Sen Mandal


Hony. Associate Editor
Your Health (2022-24)
Dr Sankar Sen Gupta


Hony. Associate Editor
Your Health (2022-24)
Dr Bibartan Saha


Hony. Secretary
Your Health (2022-24)
Dr Samrendra Kumar Basu

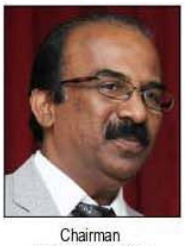
Apka Swasthya of IMA


Hony. Editor
Apka Swasthya (2022-24)
Dr Sudhir Singh


Hony. Associate Editor
Apka Swasthya (2022-24)
Dr Arun Kumar Tripathi


Hony. Secretary
Apka Swasthya (2022-24)
Dr Ritu Garg

IMA Hospital Board of India


Chairman
IMA HBI (2022-24)
Dr A K Ravikumar


Hony. Secretary.
IMA HBI (2022-24)
Dr Dinesh Bhujangrao Thakare


Treasurer IMA HBI
(2022-24)
Dr Rajeev Balkrishna Agarwal

JIMA COMMITTEE 2022-2024


Dr. Sharad Kumar Agarwal
National President, IMA
(2022-23)


Dr. R V Asokan
National President, IMA
(2023-24)


Dr. Anilkumar J Nayak
Hony Secretary General, IMA


Dr. Pradeep Kumar Nemani
Hony. Joint Secretary, Hqs


Dr. Sarbari Datta
Hony. Jt. Finance Secretary, Hqs


Prof (Dr) Nandini Chatterjee
Hony. Editor, JIMA
(2022-23)


Dr Sanjoy Banerjee
Hony. Editor, JIMA
(2023-24)


Dr Ranjan Bhattacharyya
Hony. Associate Editor,
JIMA


Dr Prasanta Kumar
Bhattacharyya
Hony. Associate Editor, JIMA


Dr. Sibabrata Banerjee
Hony. Secretary,
JIMA


Dr. Minakshi Gangopadhyay
Hony. Assistant Secretary,
JIMA


Prof (Dr) Tamonas Chaudhuri
Member, JIMA Committee


Dr Debraj Jash
Member, JIMA Committee


Dr Awadhesh Kumar Singh
Member, JIMA Committee


Dr Sekhar Chakraborty
Member, JIMA Committee


Dr. Prakash Chandra Mondal
Member, JIMA Committee

JOURNAL
Of the
INDIAN MEDICAL ASSOCIATION

Volume 121 (JIMA)
Number 10
October 2023
KOLKATA
ISSN 0019-5847

Contents

(Continued next page)

JOURNAL
Of the
INDIAN MEDICAL ASSOCIATION

Volume 121 (JIMA)
Number 10
October 2023
KOLKATA
ISSN 0019-5847

Contents

JIMA Editorial Advisory Board Members (National and International)

Editorial

Reflections on the Decade of Healthy Ageing (2021-2030) — are we ready ?

— Nandini Chatterjee
MD, FRCP (Glasgow), FICP
Professor, Department of Medicine,
IPGME&R and SSKM Hospital, Kolkata 700020 and
Hony Editor, JIMA

October 1st is being observed as the **International Day For Older Persons** since 1990, for about three decades. In this time frame, the elderly population of the globe has expanded exponentially.While in 2021, 1 in 10 people worldwide were aged 65 or above, in 2050, this age group is projected to be 1 in 6 people globally. There were nearly 138 million elderly persons in India in 2021 (67 million males and 71 million females) which is projected to increase by around 56 million elderly persons in 2031.

Population transformation is a reality in virtually every country in the world with increase in both the size and the proportion of older persons in the population. This is mainly due to the increase in life expectancy at birth that was reported to be 71.7 years on average in 2022, 25 years longer than that in 1950.Between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22%. While this population ageing – started in high-income countries like Japan, it has now involved the lower resourced countries and by 2050, 80% of older people will be living in low- and middle-income countries.

Thus it is important that we introspect - how far are we successful in "Fulfilling the Promises of the Universal Declaration of Human Rights for Older Persons" which is the UN theme of 2023 .

Are we building an age friendly and inclusive society? Do the elderly have independence, participation, self - fulfillment, care and dignity?

The answer to this question is a dismal NO in most socioeconomic strata and population subsets. **Social awareness is the need of the hour** – which includes the younger generations most importantly as well as the physician community.

In order to realize the significance of protecting the health and wellbeing of the elderly population, it is imperative that we under stand the changing physiology of the older persons and tailor our services as physicians according to their specific needs.

Geriatric Physiology :

Physiological changes occur in all organ systems with the passage of time.

Arteriosclerosis progresses while blood pressure increases and cardiac output diminishes.

The lungs show impaired gas exchange and a decrease in vital capacity.

The creatinine clearance decreases with age and so does the eGFR.

Altered hepatic drug metabolism and GI dysmotility are common in the elderly leading to altered bowel habits. Impaired glucose regulation occurs with age due to multifactorial pathophysiology and osteoporosis is a natural accompaniment caused by decline in bone mass.

The epidermis of the skin atrophies with lossof tone and elasticity, loss of muscle mass leads to frailty. Degenerative changes occur in many joints and this, combined with the loss of muscle mass, hampers the mobility and functional status of the older person.

These age related changes have significant bearing onActivities of daily living (ADLs) that are needed for basic self-care. Instrumental ADL (IADLs) are tasks that are physically and cognitively more difficult than self-care tasks and are necessary for independent living in the community. ADLs and IADLs are measures of disability and limitations of an elderly person in functioning in family and society.

Geriatric Morbidity Pattern :

Apart from the physiological alterations , elderly are prone to develop chronic diseases which often coexist and are interrelated – a phenomenon called multimorbidity. The list of common conditions i.eHypertension, heart disease, arthritis,cancer,chronic Kidney Disease Chronic Obstructive Pulmonary Disease, Dementia, Alzheimer's Disease, diabetes, Osteoporosis and Stroke may occur in any permutation and combination and inevitably lead to polypharmacy and its inherent risks of drug related adverse events and interactions. Heart disease is by far the most common cause of death, followed by cancer. The five leading causes of death in the elderly - heart disease, cancer, stroke, chronic lower respiratory tract disease, and Alzheimer's disease-account for 69.5% of all deaths.

Geriatric Assessment :

In order to provide holistic patient care, a meticulous evaluation of the patient is necessary. However, comprehensive Geriatric assessment is a distinct field of its own that needs awareness and training on the part of the physician. This aids in the diagnosis, development of treatment and follow-up strategies as also management of long-term care needs .

The geriatric assessment differs from a standard medical evaluation by including nonmedical domains like functional capacity, quality of lifeand psychosocial issues.

It requires a multidisciplinary team to assess specific elements of physical health including nutrition, vision, hearing, cognition, fecal and urinary continence, and balance.

Well-validated tools and survey instruments for evaluating activities of daily living are available for comprehensive assessment – but it requires patience and commitment of the assessor as well as consent and co operation from the patient or caregiver.

Geriatric Treatment Strategies :

The management protocols for elderly patients should also take into account of the fact that metabolism is altered which changes the pharmacokinetic and pharmacodynamic equations of commonly used drugs.

Drug dosages need to be individualized according to comorbidities present and a high degree of clinical suspicion is to be kept for detection of adverse drug reactions to avoid prescribing cascades.

Rational preventive programs of **diet, exercise and vaccinations** too are to be integrated with pharmacotherapy.

To conclude,

All older persons are not Super Agers, a term coined in recent years to designate healthy agers who in their 70s and 80s have the mental or physical capability of their much younger counterparts.

They are to be nurtured with dignity utilizing improved and targeted approaches that incorporate long-term and holistic care. Supportive empathetic environments induce elderly individuals to function better and maintain their independence as they age.

Older persons have the wisdom and experience that can contribute towards building up of a productive, peaceful and cohesive society. We must ensure their physical and mental wellbeing, active participation, and effective contributions to their environment through medical, social and workplace policies addressing geriatric issues.

Further Readings

1 Gerstenblith G, Lakatta EG, Weisfeldt ML — Age changes in myocardial function and exercise response. *Prog Cardiovasc Dis* 1976; **19(1):** 1-21.

2 Portman OW, Alexander M — Changes in arterial subfractions with aging and atherosclerosis. *Biochim Biophys Acta* 1972; **260(3):** 460-74.

3 Muiesan G, Sorbini CA, Grassi V — Respiratory function in the aged. *Bull Physiopathol Respir (Nancy)* 1971; **7(5):** 973-1009.

4 Brody AW, Johnson JR, Townley RG, Herrera HR, Snider D, Campbell JC — The residual volume: predicted values as a function of age. *Am Rev Respir Dis* 1974; **109(1):** 98-105.

5 Dunnill MS, Halley W — Some observations on the quantitative anatomy of the kidney. *J Pathol* 1973; **110(2):** 113-21.

6 Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR — Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. *N Engl J Med* 1980; **303(21):** 1195-8.

7 Gilchrest BA — Some gerontologic considerations in the practice of dermatology. *Arch Dermatol* 1979; **115(11):** 1343-6.

8 Rebeiz JJ, Moore MJ, Holden EM, Adams RD — Variations in muscle status with age and systemic diseases. *Acta Neuropathol* 1972; **22(2):** 127-44.

Original Article

Analysing the Ocular Emergencies Presenting at a Tertiary Eye Hospital in Western India During the Second Wave of COVID Pandemic

Shivani Chetan Hindocha[1], Reema Raval[2], Kintu Shah[3], Rutul Patel[4]

Aims and Objectives : To understand the frequency and types of ocular emergencies presenting to a Tertiary Eye Hospital in Western India, during the 2nd wave of the COVID Pandemic.

Materials and Methods : Study Design – Longitudinal cross sectional study. Sample Size – 1087.

Duration – 5 months. Site – Tertiary Eye Institute at Ahmedabad (Gujarat)

Inclusion Criteria – All patients who presented to our institute during emergency hours.

All the data was collected on demography, clinical examination and diagnosis and immediate treatment that was given.

Results : Out of 1087 patients, 848 (78%) had Traumatic and 239(22%) had Non-traumatic emergency. Among the trauma cases, 73% had closed globe injury, with majority being due to corneal foreign bodies. Majority presented within 24 hours of the trauma. Among the Non-traumatic emergencies, Conjunctivitis was commonest (136 cases). But the sudden avalanche of Orbital Mucormycosis (28 cases) was the biggest challenge of the 2nd wave of the COVID Pandemic.

Other causes of painful red eye, such as corneal ulcer, subconjunctival haemorrhage, iridocyclitis, acuteattack of angle-closure glaucoma also presented earlier within 24 hours of onset of symptoms.

Conclusion : Due to the unlock during the 2nd wave of the COVID pandemic in India we saw an increase number of closed globe injuries at our Tertiary Eye hospital in Western India.

Among the Non-traumatic emergencies, patients with red eye presented in large numbers due to the fear of Mucormycosis and 28 of them actually turned out to be positive.

[*J Indian Med Assoc* 2023; **121(10):** 14-7]

***Key words* : Ophthalmic Emergency, COVID Pandemic, Closed Globe Injury, Open Globe Injury, Red Eye, Mucormycosis.**

The COVID-19 pandemic, which started at Wuhan in China, in November, 2019 and had spread globally very rapidly, has had a drastic effect on the health and lives of the human population. Each wave of the pandemic had a different feature and its impact varied even in different parts of a large country like India.

Ophthalmic emergencies present to Tertiary Hospital more in numbers as patients come directly and are also mostly referred from primary centres.

During the unprecedented times of COVID pandemic, eye hospitals across India have seen a paradigm shift in the class of patients presenting to them and the various manifestations related to COVID.

Aims and Objectives

To understand the frequency and type of ocular emergencies presenting to our Tertiary Eye Hospital at Ahmedabad (Gujarat) in Western India during the 2nd wave of the COVID pandemic.

Editor's Comment :

- During the COVID-19 pandemic and the lockdown rules, many patients choose to stay indoor inspite of having ocular pathologies which resulted in delay in treatment. Also avoid overdosage of steroids during COVID-19 which may increase mucormycosis cases.

Material and Method

The C H Nagri Eye Institute is a Tertiary Multi Speciality Eye Institute, managed by the Ahmedabad Municipal Corporation and is attached to the NHL Medical College, Ahmedabad. The hospital, in addition to serving the population of Ahmedabad city, also functions as one of the two tertiary eye care centres for the whole of Gujarat and for neighbouring states of Rajasthan and Western part of Madhya Pradesh. We conducted a Longitudinal Cross Sectional study at our Tertiary Eye Institute, during a period of 5 months from 1st March, 2021 to 30th July, 2021 covering the major period of the 2nd wave of the COVID pandemic in India.

Department of Ophthalmology, Smt NHL Municipal Medical College, Ahmedabad, Gujarat 380006

[1]MBBS, Resident and Corresponding Author

[2]MS (Ophthalmol), Professor

[3]MS (Ophthalmol), Associate Professor

[4]MBBS, Resident

Received on : 06/11/2022

Accepted on : 21/01/2023

The inclusion criterion was of all patients who presented to our Ophthalmic emergency services during the above mentioned period. The study adhered to tenets of the Declaration of Helsinki. No identifiable parameters of patient information were used for data analysis.

A total of 1087 patients were enrolled in this study. A detailed history of all these patients was taken.Patients underwent a detailed clinical examination including visual acuity, slit lamp examination, Non contacttonometry ,Fundus examination, assessment of Ocular movements.

Observations

A total of 1087 patients were seen during our study period, of which 956(88%) were Males and 131(12%) were Females. 848(78%) cases were Traumatic emergencies and 239(22%) were Non-traumatic emergencies.

Of the Traumatic injuries, 619(73%) cases were Closed Globe Injury and 229(27%) cases were Open Globe Injury.

Majority of the patients of Closed Globe Injuries, ie, 417 cases were in the active working age group of 20 to 40 years. 76 cases were less than 20 years old and 126 patients were 40 years and older. 537 patients who presented with closed globe injury, had a conjunctival / corneal foreign body, 31 patients had photokeratitis due to exposure to welding arc, 18 had chemical injuries, 16 had ecchymosis due to blunt trauma, 15 had lacerations and lid tears and 2 presented with blow out fractures (Fig 1).

Type of Closed Globe Injuries :

106 patients who presented with Open Globe Injuries were less than 20 years of age, 70 patients were in the age group of 20 to 40 years and 53 patients were 41 years and above.

72% of patients with Closed Globe Injuries presented to us within 24 hours of the injury while 94% of Open Globe Injuries presented to us within 24 hours of the injury.

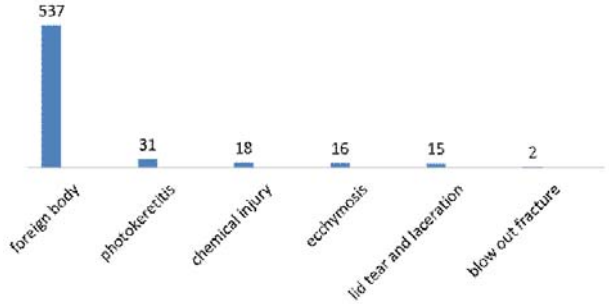


Fig 1 — Type of Closed globe injury

Time of presentation of closed Globe Injury (Fig 2):

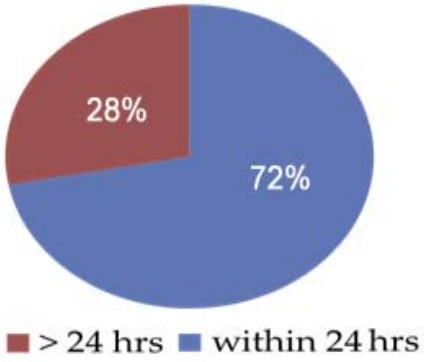


Fig 2 — Time of presentation of Closed Globe Injury

Time of presentation of open Globe Injury (Fig 3) :

239 patients presented to our emergency clinic during the study period with Non-traumatic ophthalmic emergencies of which, 136 cases were of red eye due to conjunctivitis, 23 cases were of corneal ulcer, 15 cases were of iridocyclitis, 15 cases were of subconjunctival haemorrhage and 11 cases were of acute attack of angle closure glaucoma. We saw 28 cases of Mucormycosis related orbital cellulitis during this period. Apart from this, 11 patients presented to us with loss of vision due to retinal vascular occlusion or vitreous haemorrhage or Postoperative Endophthalmitis.

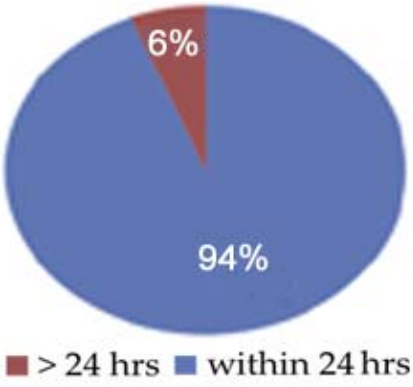


Fig 3 — Time of presentation of Open Globe Injuries

Type of Non Traumatic Emergencies (Fig 4) :

Majority of patients ie, 188 cases who presented with Non-traumatic emergencies due to Red Eye of various causes were in the age group of 20 to 50 years. 28 cases were less than 20 years of age. 23 patients were 51 years and above.

We observed a spike of Orbital Mucormycosis patients (28 cases) presenting during this short study period of the 2nd wave of the COVID-19 pandemic. 25

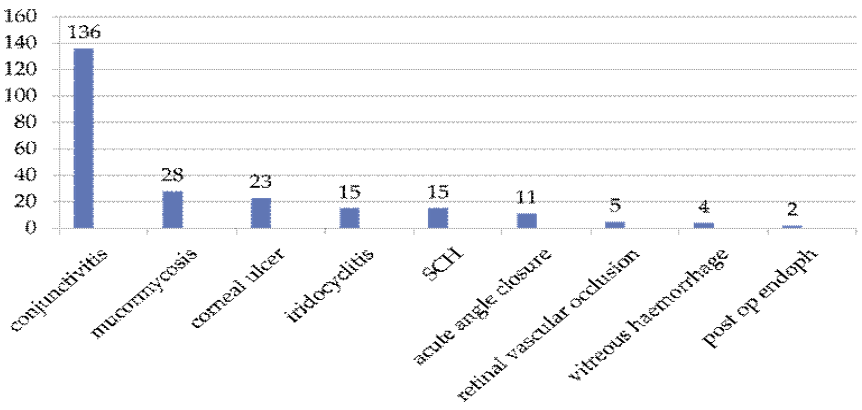


Fig 4 — Type of Non-traumatic Injuries Emergencies

patients were 40 years and above while 3 were in the age group of 20 to 40 years but none in the below 20 years age group.

Age group in Mucormycosis Patients (Fig 5) :

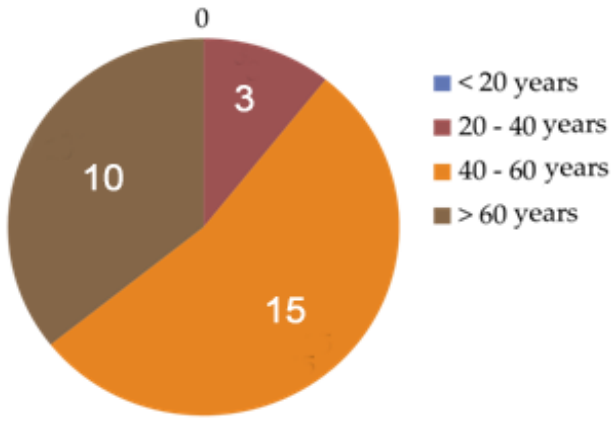


Fig 5 — Age group of Mucormycosis patients

Discussion

Our tertiary Eye Institute in Ahmedabad saw a very high number of traumatic and Non-traumatic ophthalmic emergencies during the 2nd wave of the COVID-19 pandemic in 2021 in India which could be partly attributed to the fact that many Government and private hospitals had been totally converted into COVID hospitals during this period and many individual private practice setups were not accepting emergencies leading to a centralization of Ophthalmic Emergency Services[1,2].

We saw 56.9 % cases being traumatic injuries due to minor corneal foreign bodies (49.4%) and welding are induced photokeratitis (2.85%), surface chemical injuries (1.65%) or adnexal injuries(3%)which can be attributed to the injuries at workplace or while doing household chores since the lockdown in India in 2020 and the burden of the 1st wave of the COVID-19 pandemic had created a compulsion for the continuance of industrial work and small businesses in 2021, inspite of the medical situation of the pandemic. However agricultural injuries were minimal.

In a study, Pellegrini, *et al* observed 354 eye injuries (15.6% of emergency admissions) in 2019 between March 10 and April 10, while 112 eye injuries (19.9% of all ED presentations) were noted in the same interval in 2020. They found that during quarantine, the proportion of children and adolescents with ocular injuries decreased (from 14.7% to 8.0%) and that the proportion of men increased (from 66.7% to 75.0%). They showed a dramatic reduction in eye injuries (68.4%) during the pandemic period, and predicted that behavioral changes at the time of quarantine would decrease the risk of trauma. They stated that the decrease in sports injuries and injuries in children during school closure supports this hypothesis[4]. In our study, out of the 848 eye injuries, 75 cases (8.84%) of Open Globe Injuries and 106 cases (12.5%) of Closed Globe Injuries were found to be in children and adolescents which could be attributed to the inability of the Government to impose a very strict lockdown during this period.

Most of the trauma patients reached our emergency centre quite early- 72 % of closed globe injuries and upto 94% of Open Globe Injuries- within 24 hours of the injury as Ophthalmic Emergency services had been centralized during this period and there was no lockdown as had been the situation during the same period in 2020 in India[6]. This enabled an earlier and more efficient management of all these trauma cases.

Among the Non-traumatic emergencies, conjunctivitis was commonest (56.6%) as compared to 29.4% at a hospital in Sao Paulo, Italy[4] during the COVID-19 pandemic period and 13.19% at a Tertiary Eye Centre (Shankar Netralaya) in South India in 2020[5]. We attribute this to the poorer social distancing in India during the second wave and also the extreme rise of Mucormycosis cases in Gujarat which caused a panic situation wherein all cases of Red Eye like conjunctivitis, iridocyclitis, corneal ulcers, acute attacks of angle closure glaucoma and even

subconjunctival haemorrhage rushed to tertiary eye institutes to rule out this grave condition. We actually did see 28 cases of Orbital Mucormycosis during this period who were either, diagnosed elsewhere and referred in emergency for management,or were primarily diagnosed at our institute. Most of these patients were above the age group of 20 years. This data is comparable to the Collaborative OPAI – IJO study[3] and a study by Walia S, *et al*[7].

We noticed that other Non-traumatic Ophthalmic emergencies like retinal vascular occlusions,vitreous haemorrhage and Postoperative endophthalmitis were also referred to our tertiary institute during this period as routine Ophthalmic services were disturbed at many centres.

Conclusions

In conclusion, due to the unlock during the second wave of the COVID pandemic in India we saw an increase number of Closed Globe Injuries at our Tertiary Eye Hospital in Western India .

Among the non traumatic emergencies, patients with Red Eye presented in large numbers due to the fear of Mucormycosis and 28 of them actually turned out to be positive.

Financial support and sponsorship : Nil.

Conflicts of interest : There are no conflicts of interest.

References

1 Nair AG, Gandhi RA, Natarajan S — Effect of COVID-19 related lockdown on ophthalmic practice and patient care in India: Results of a survey. *Indian J Ophthalmol* 2020; **68:** 725-30.

2 Sengupta S, Honavar SG, Sachdev MS, Sharma N, Kumar A, Ram J, *et al* — All India Ophthalmological Society–Indian Journal of Ophthalmology consensus statement on preferred practices during the COVID-19 pandemic. *Indian Journal of Ophthalmology* 2020; **68(5):** 711.

3 Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, *et al* — Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India–Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian Journal of Ophthalmology* 2021; **69(7):** 1670.

4 Pellegrini M, Roda M, Lupardi E, Di Geronimo N, Giannaccare G, Schiavi C — The impact of COVID 19 pandemic on ophthalmological emergency department visits. Actaophthalmologica.2020 Dec 1.

5 Pal SS, Alam MS, Giratkar SM, Mukherjee B — Analysis of ophthalmic emergency visits during COVID-19 Lockdown in a tertiary eye care center in South India. *TNOA Journal of Ophthalmic Science and Research* 2022; **60(1):** 2.

6 Agrawal D, Parchand S, Agrawal D, Chatterjee S, Gangwe A, Mishra M, *et al* — Impact of COVID-19 pandemic and national lockdown on ocular trauma at a tertiary eye care institute. *Indian Journal of Ophthalmology* 2021; **69(3):** 709.

7 Walia S, Bhaisare V, Rawat P, Kori N, Sharma M, Gupta N, *et al* — COVID-19-associated mucormycosis: Preliminary report from a tertiary eye care centre. *Indian Journal of Ophthalmology* 2021; **69(12):** 3685.

Original Article

Clusters of Varicella Zoster in the Tribal-dominated District of Western India : An investigation Report

Vikram Khan[1], A A Sanghai[2], Jerin Rajan[3], Atul Kumar Sharma[4], Sanket Nayak[5], V K Das[6]

Background : Chickenpox is an infectious disease caused by the Varicella Zoster Virus (VZV). It is very contagious and spreads by inhaling infected droplets. It is generally found in epidemic waves, the most common victims are school-going children but outbreaks of chickenpox are also reported in adulthood.

Objectives : The outbreak investigation in two different age groups were investigated to identify the agent, the source of infection and to propose recommendation for control measures.

Methods : In the present investigation, we are analyzing the epidemiological determinants of two chickenpox clusters reported from the tribal-dominated district of the Union Territory of Dadra and Nagar Haveli and Daman and Diu, India.

Results : Both clusters have single-pick, confirmed clinically as well as in the laboratory as per the protocol. All the cases of clusters were self-limiting and recovered within 4-5 days.

Interpretation and Conclusion : The study emphasizes the quality disease surveillance mechanisms can play a critical role in providing accurate and timely information to authorities, allowing for early intervention and outbreak management.

[*J Indian Med Assoc* 2023; **121(10):** 18-22]

Key words **: Varicella-zoster, Chickenpox, Outbreak, Disease Surveillance.**

Chickenpox is a contagious acute viral disease caused by Varicella Zoster Virus (VZV) of the Herpesviridae family[1]. It is generally found in epidemic waves[2]. It is transmitted by direct contact or airborne. The shedding of pathogen happens from the nasopharynx via droplets and aerosols and also from skin lesions[3]. The mild skin lesions or skin rash is the main symptom of the disease but hospitalization and death can also be occurred due to complications such as pneumonitis, encephalitis, and secondary bacterial infections[4]. The disease is usually self-limiting and can be cured in 5 to 10 days without complications[5]. The risk of complications from varicella is more in the high-risk groups (eg, immunocompromised persons, cancer patients, pregnant women, and neonates whose mothers are not immune). The incubation period of the disease is usually 14-16 days. The contagious period starts from 1-2 days before the onset of symptoms and appears up to 5-7 days. In the absence of vaccination, the incidence of varicella in tropical countries is encountered 13-16 cases per 1000 people annually[6]. The highest incidence occurs in pre-school and school children between the age of 1 to 6 years but can also occur in adults[5,7,8]. Seroconversion of Varicella-Zoster Virus can occur in late adulthood in the tropical countries[9]. Various researchers has document that the outbreaks of chickenpox globally are in school going children[7,10]. However, Country like India the outbreaks can be occurred in adulthood [11,12] and also in the school going children[13-16]. For the prevention of the chickenpox, the Indian Academy of Pediatrics have recommended the vaccination of chickenpox with two doses, one at the age of 15 months and the second between 4 to 5 years of age[17]. But in India, the vaccination of Chickenpox is still optional and not included in the National Immunization Schedule under Universal Immunization Programme. In the present investigation, we are investigating the epidemiological determinants of two Chickenpox

Editor's Comment :

- The present study is a lesson to learn that the Chickenpox vaccine should be considered for inclusion in the routine immunization schedule.

Directorate of Medical Health Services, Silvassa, Dadra & Nagar Haveli and Daman and Diu 396230

[1]PhD, Public Health Expert, State Surveillance Officer, Integrated Disease Surveillance Program and Corresponding Author

[2]MVSc, State Veterinary Consultant of Integrated Disease Surveillance Program, UT of DNH & DD

[3]MSc, Assistant Professor, Department of Medical Surgical Nursing, Shri Vinoba Bhave College of Nursing, Silvassa, Dadra and Nagar Haveli and Daman and Diu 396230

[4]MTech, State Data Manager, Department of Integrated Disease Surveillance Programme

[5]BDS, Epidemiologist, Integrated Disease Surveillance Program, UT of DNH & DD

[6]MBBS, Director, Directorate of Medical & Health Services, UT of DNH & DD

Received on : 03/10/2022
Accepted on : 10/01/2023

clusters which are reported from the tribal-dominated district of Dadra and Nagar Haveli of the Union Territory of Dadra and Nagar Haveli and Daman and Diu.

Materials and Methods

Study Area :

The district of Dadra Nagar Haveli (D&NH) is situated (Latitude, 20°54'41" N to 20°21'36" N and Longitude– 72°54'41" N to 73°13'13" N) in the Western Ghat of India. The 487 sq km area is a forest hill area, occupied mainly by tribes (population 4.5 lakh) in 72 villages and one town. Due to the subsidies in taxes, a large number of industries have been established in this district in the last decades. As a result, around 2.5 lakh of skilled and unskilled workforce migrate to D&NH from different states of India for the employment. The present incidences were reported from the tribal-dominated village of Surangi (located at 20°09'19.1"N,73°00'43.7"E.) and Dapada (20°11'10.64"N, 73°1'10.61"E) of the district D&NH. In both the villages, along with the tribal majority population, due to industrial units migratory population also exists together especially in chawls / overcrowded residence. The Primary health facilities for the residents of these villages are provided by Health and Wellness Centres (HWCs) and the Primary Health Centres (PHCs) which is located in the village itself. The total geographical area of the village Surangi and Dapada is 1012.97 and 856.41 hectares and the total population of these two areas is 5,016 and 5713 respectively. The locations of hot spot are showing in the Fig 1.

Diseases Surveillance Mechanism :

The portal-based, three-tier surveillance of Chickenpox under Integrated Diseases Surveillance Programme (IDSP) was going on since the year 2009. In this system, both active and passive surveillance was done. During active Surveillance, the grass root level workers do syndromic surveillance from house to house and the information about the patients are entered in to the portal. Apart from this, the Clinicians are involved in the presumptive surveillance and the information about clinically suspected Chickenpox patients who visit to their dispensary are recorded and shared with the portal. Chickenpox can be defined as "An acute illness with diffuse (generalized) macular/ papular vesicular rash and Epidemiologic linkage to another probable or confirmed case or Laboratory confirmation by VZV-specific IgM antibodies detection or VZV DNA detection by PCR or isolation of Chickenpox Virus from a clinical specimen." This definition was used for the surveillance of chickenpox and is investigated by the Medical Officer working at the PHC and also by Rapid Response Team (RRT) during the outbreak or during period of early warning. The similar case definition was used to identify chickenpox among children and adults (≥15 years). The samples (ie, serum, blister/skin swab, urine and throat swabs) from the clinical suspected cases were collected and referred to the laboratory for the confirm / final diagnosis.

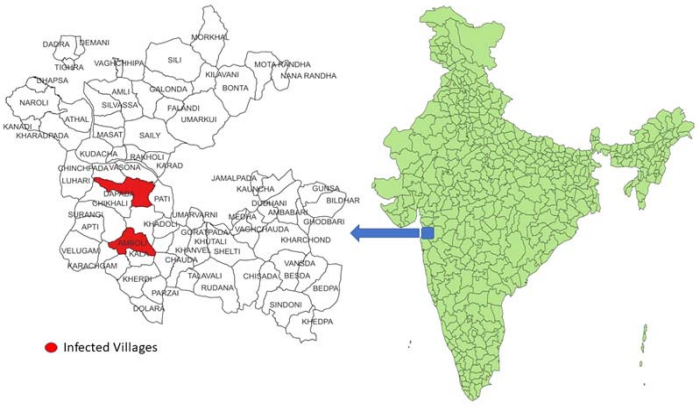


Fig 1 — The GIS Map is showing the location of Clusters reported from the District Dadra Nagar Haveli

Cluster Investigation :

As the early warning signal/cluster was identified, the RRT of the district visited the hot spot and initiates the investigations. The survey was conducted among the affected population to find each suspect / probable case as per the standard case definition. All the patients having symptoms of an acute illness with diffuse (generalized) macular/papular vesicular rash were examined by the clinician and they were purposefully isolated from each other to prevent transmission. Furthermore, the passive data of indoor and outdoor patients along with laboratory results were collected from the concerned health institutions. Daily surveillance was conducted in adjoining areas and all the epidemiological information was recorded in standard case investigation form. The high-risk groups (eg, immuno-compromised persons, cancer patients, pregnant women and neonates whose mothers are not immune) were also identified and sensitized about the preventive aspect of the disease. The surveillance was conducted daily for 6 weeks from the date of the last reported case.

Laboratory Investigation :

Twenty serum samples were obtained from the symptomatic patients (7 samples were collected from village Dapada and 13

samples were collected from the village Amboli) after oral consent from the patients or guardians and sent to the National Institute of Virology Pune for laboratory investigation and confirmation of by ELISA IgM antibody. The results were documented as per the cut of values of titer prescribed on the kit.

Results

Cluster 1 :

A few cases of Chickenpox were reported from Surangi village of Amboli PHC during routine surveillance by health workers on 22/02/2022. The report was in-depth studied and the rapid response team was activated on the same day by IDSP. The hotspot was an industrial Chawl with 37 rooms (typically low-quality housing). A total of 250 migratory laborers residing in this Chawl had come from other states of India to work. This chawl had the facilities of common toilets and bathrooms. Most of the residents were young men and lived in a room with 5-8 people. Only 4 people lived with their families. The index case was reported on dated 30/01/2022, he was a 5-year-old male with having travel history and came from the northern part of India. The rest of the positives were close contacts of the index case. Total 23 cases with the same symptoms were counted from 30/01/2022 to 21/02/2022, out of the total 91.30% (21 cases) belonged to the age group of > 15 years and 8.70% (2 cases) belong to the age group of 0-5 years. All cases were male. All patients were clinically stable, treated on the basis of symptoms, no one required hospitalization and were cured without any complication. The vaccination status of residents was unknown. A total of seven serum samples were collected from the affected area as per the protocol of the IDSP and sent to the referral laboratory for lab confirmation.

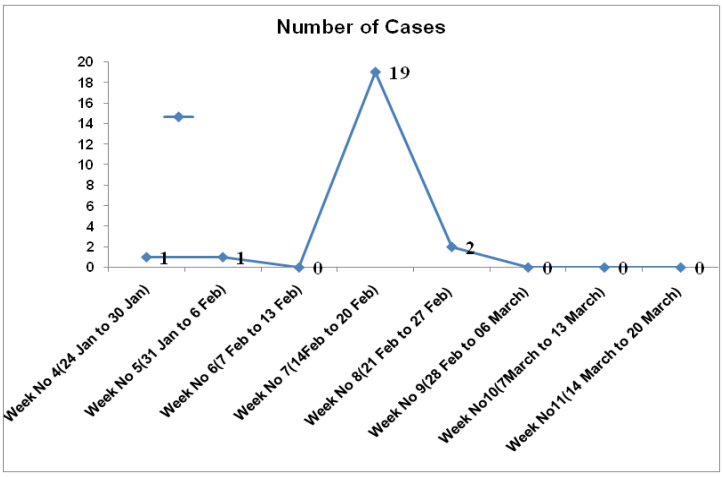


Fig 2 — Showing the timeline of onset of symptoms in Cluster 1 reported from the Surangi Village

All samples were found positive in the laboratory through ELISA IgM antibody. Active surveillance was conducted in the village and adjoining areas through grassroots health workers, but no more suspected cases were found. The area was kept under surveillance till the completion of the double incubation period of diseases. The timeline of cluster 1 is described in Fig 2 and the variables of the cluster are explained in Table 1.

Cluster 2 :

The notification of the second cluster was received on 08/07/2022 from the village Dapada, PHC Dapada by the Principal of the residential school. As per the protocol of IDSP, the Rapid response team visited the affected area on the same day, along with the concerned Medical Officer and Health Workers. It was a hostel with two separate buildings, 120 girls lived in one building. 117 boys lived in the second building. 4-6 students were staying in each room. The toilet and bathrooms of the students were separate in each

Table 1 — *Showing the determinates of the Clusters of Varicella Zoster reported from the D & NH*

Particulars	Cluster 1, Village-Amboli					Cluster-2, Village-Dapada				
	Age			Sex		Age			Sex	
	0-5 Year	6-15 Year	≥15 years	Male	Female	0-5 Year	6-15 Year	≥15 years	Male	Female
Total Population of Village	402	774	3480	2362	2294	365	959	4729	3305	2745
Population at risk	8	9	233	237	7	0	166	71	117	120
Total Incidence	2	0	21	23	0	0	12	27	28	11
Attack rate/100 population	25.00	0.00	9.01	9.70	0.00	0.00	7.23	38.03	23.93	9.17
Persons with specimens collected	0	0	7	7	0	0	0	13	9	4
Laboratory confirmation	0	0	7	7	0	0	0	4	3	1
Need of Treatment	2	0	19	21	0	0	8	19	21	6
Hospitalization	0	0	0	0	0	0	0	0	0	0
Mild Symptoms	0	0	2	2	0	0	4	8	7	5
Moderate Symptoms	2	0	19	21	0	0	8	19	21	6
Severe Symptoms	0	0	0	0	0	0	0	0	0	0
Vaccination Status	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Average Duration of Illness	4.5 days	0	4.90 days	4.87 days	0	0	4.75 days	4.85 days	4.82 days	4.81 days

building. All students used the common kitchen to eat the food. On 8th July 2022, all the children living in the hostel were examined by the concerned Medical Officer, in which a total of 18 more children were found with similar symptoms. After that, sporadic cases were encountered till 26th July, 2022. The timeline of Cluster 2 is shown in Fig 3. The children who were symptomatic were immediately isolated for at least 7 days from the date of onset. The children and the hostel warden were made aware of the symptoms, mode of transmission, serious conditions of the disease and methods of prevention of this disease. The active surveillance in the surrounding areas was conducted by the grassroots level health workers but no more case with similar symptoms was encountered.

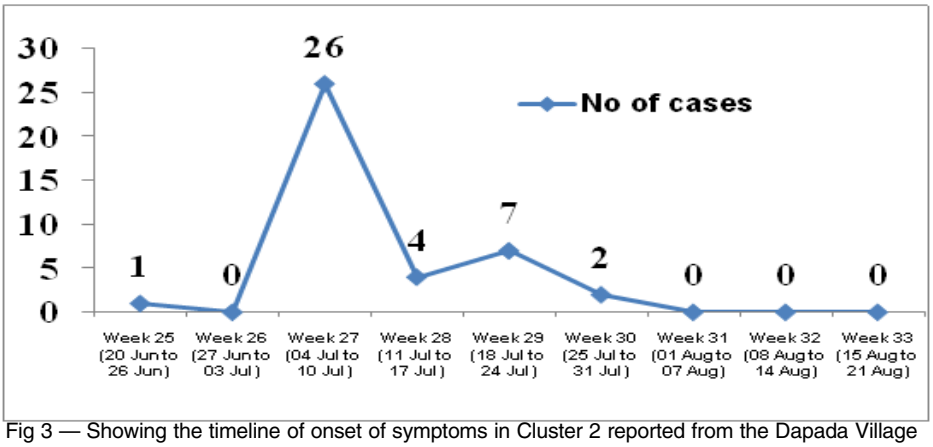


Fig 3 — Showing the timeline of onset of symptoms in Cluster 2 reported from the Dapada Village

During the investigation, it was found that a 12-year-old boy, who had traveled to Maharashtra, first showed signs of Chickenpox. Therefore, he was considered an index case. It was a single-pick outbreak and restricted up to a hostel in which, 69.23% of cases belonged to the age group of 5 to 9 years and 30.77% of cases were belong to the age group of 10 to 15 years. The last case from this place was reported on 26/07/2022. Therefore, the area was kept under surveillance till the completion of the double incubation period of diseases as per the protocol of IDSP. All the patients were treated symptomatically; no patient required hospitalization, and all the cases were cured without any complications. Total 13 serum samples were collected from the clinically confirmed patients and sent to the referral Laboratory for lab confirmation. Out of the total samples, 4 samples were confirmed Varicella Zoster through the IgM ELISA method. The epidemiological variables of both clusters prescribe in Table 1.

Discussion

The present study describes above the epidemiological determinants of the Chickenpox clusters encountered in the tribal district of Dadra & Nagar Haveli in the year 2022. The Cluster 1 was noted from the industrial area (Chawl) and the Cluster 2 was encountered from the student's residential hostel. Due to prompt identification, investigation and control measures, it was possible to restrict these clusters to limited areas, smaller sizes and shorter duration. Both clusters were confirmed by the clinically and the Laboratory reports. A significant difference was observed in the age of the infected persons in both the clusters. In the Cluster 1, most of the infected person belong to the age group of above15 years, whereas in the Cluster 2, maximum cases were noted in the age group of below 15 years. Outbreaks of Chickenpox are common in Worldwide[2,7,9]. Recently, the outbreaks of Chickenpox have been reported from various States of India like Jharkhand[16,18]; Assam[19]; Tamilnadu[8]; Himachal Pardesh[13]; Kashmir[14]; Chandigarh[6]; Odisha[20]. The district of Dadra and Nagar Haveli also has a history of outbreaks due to the circulation of Clade-1 VZV[15,21]. Most authors agree that the transmission of chickenpox follow a seasonal pattern, Varicella virus reduces their transmissibility in high temperatures, the causes of the seasonal transmission may be environmental or social in nature[10]. In the district of Dadra Nagar Haveli, the outbreaks of Chickenpox was normally been encountered in the month of December to February of the year of 2016-17, when the outbreak was common it happens in the same period only[21]. But in the present investigations, the time of Outbreaks were note between January and July month. This indicates that the seasonality of the outbreak of Chickenpox is changing. The migratory population, close proximity of living, overcrowding environments and increased social interactions elevated the rate of transmission of the disease[1]. The present clusters of Chickenpox were also started from immigration of a viremic migrate and the others attributed factors of these clusters are as explained above. Normally the outbreaks of Chickenpox have been reported in ages ranging from pre-school children to adults[16]. In this study a difference has been seen in the age of the infected. In the first cluster, most of the infected persons belong to the age group above 15 years, whereas, in the second cluster, most of cases

were in the age group of below 15 years. The outbreaks of Chickenpox were confirmed on the basis of clinical presentations with the help of serological tools, molecular tools and a combination of serological and molecular tools in the laboratory (Singh, *et al* 2015; Vaidya, *et al* 2018; Kerketta, *et al* 2019; Kujur, *et al* 2022)[6,15,16,20]. In this outbreaks events the cluster were identified by their clinical presentations and confirmed by the serological reports obtained from NIV Pune.

Conclusion

Chickenpox is a Vaccine-preventable disease; it is mostly affected the age group from pre-school and less among adults. Due to self-limiting in nature, the disease is mostly neglected. Every year, outbreaks of Chickenpox are reported from different locations in India. In the absence of Chickenpox vaccination in routine immunization schedules of the country, effective surveillance mechanisms and cluster management are the only ways to restrict the risk for exposure. The result of the study also emphasis that there are equal chances of transmission among adults as well as children. The capacity building of the stakeholders like caretakers, teachers and hostel warden may also be helpful to the early detection of warning signals.

Acknowledgement

We thank to the Director, Medical & Health Services, UT of Dadra & Nagar Haveli and Daman & Diu and the Integrated Disease Surveillance Programme for providing necessary support. The study is a part of routine surveillance under the Integrated Disease Surveillance Programme.

Conflict of Interest : The authors declare no personal or financial conflict of interest.

Financial Support : The authors declared no financial support.

References

1 Misra V, Gawali D, Jain AK, Khetan R, Jain SB — Acute Rise in the Incidence of Chickenpox due to Temperature Variation in a Specific Locality of Gwalior City. *Indian J Community Med* 2021; **46(2):** 323-4. doi: 10.4103/ijcm.IJCM_156_20. Epub 2021 May 29. PMID: 34321753; PMCID: PMC8281847.

2 Loparev V, Marto E, Rubtcova E — Toward Universal Varicella-Zoster Virus (VZV) Genotyping: Diversity of VZV Strains from France and Spain. *Journal of Clinical Microbiology* 2007; **45(2):** 559-63.

3 Centers for Disease Control and Prevention. Chickenpox (varicella). (2021).

4 Varela FH, Pinto LA, Scotta MC — Global impact of varicella vaccination programs. *Hum Vaccin Immunother* 2019; **15(3):** 645-57. https://doi.org/10.1080/21645515.2018.1546525 PMID: 30427766

5 Heininger U, Seward JF — "Varicella," *Lancet* 2006; **368(9544):** 1365-76.

6 Singh MP, Chandran C, Sarwa A, Kumar A, Gupta M, Raj A, Ratho RK — Outbreak of chickenpox in a Union Territory of North India. *Indian Journal of Medical Microbiology* 2015; **33(4):** 524-7.

7 Zhang X, Yu Y, Zhang J — The epidemiology of varicella cases among children in Beijing's Fengtai District from 2008 to 2012. *Vaccine* 2014; **32(29):** 3569-72.

8 Meyers J, Logaraj M, Ramraj B, Narasimhan P, MacIntyre CR — Epidemic Varicella Zoster Virus among University Students, India. *Emerg Infect Dis* 2018; **24(2):** 366-9. doi: 10.3201/eid2402.170659. PMID: 29350152; PMCID: PMC5782884.

9 Garnett GP, Cox MJ, Bundy DAP — The age in infection with varicella zoster virus in St Lucia, West Indies. *Epidemiology and Infection* 1993; **110:** 361-72.

10 Noha Saleha and Bassem Al Moghazyb. Seasonal variation and trend of chicken pox in the southern region of Saudi Arabia (2007–2012). *J Egypt Public Health Assoc* 2014; **89:** 143-7.

11 Balraj V, John TJ — An epidemic of Varicella in rural southern India. *J Trop Med Hyg* 1994; **97:** 113-6.

12 Sinha DP — Chickenpox-a disease predominantly affecting adults in rural West Bengal, India. *Int J Epidemiol* 1976; **5:** 367-74.

13 Gupta SN, Gupta N and Gupta S — Concurrent multiple outbreaks of varicella, rubeola, German measles in unvaccinated children of co-educational mount Carmel senior secondary school, Thakurdwara Palampur of northern Himachal, India. *Journal of Family Medicine & Primary Care* 2015; 117-23.

14 Kadri SM, Rehman S. Rehana K — Rising Trends of Chicken Pox Outbreaks among School Children in Kashmir, India-Suggestions for Health Policy. *EC Bacteriology and Virology Research* 2.5. 2017: 179-90.

15 Vaidya SR, Tilavat SM, Kumbhar NS, Kamble MB — Chickenpox outbreak in a tribal and industrial zone from the Union Territory of Dadra and Nagar Haveli, India. *Epidemiology and Infection* 2018; **146:** 476-80. https://doi.org/10.1017/S0950268818000201

16 Kujur A, Kiran K, Kujur M — An Epidemiological Study of Outbreak Investigation of Chickenpox in Remote Hamlets of a Tribal State in India. *Cureus* 2022; **14(6):** e26454. DOI 10.7759/cureus.26454

17 Vashishtha VM, Choudhury P, Kalra A, Bose A, Thacker N, Yewale VN, *et al* — Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 years – India, 2014 and Updates on Immunization. *Indian Pediatr* 2014; **51:** 785-803.

18 Pall S, Kumar D — Outbreak investigation of viral exanthem in Jharkhand, India: an eye opener for surveillance managers and vaccine policy makers. *Int J Community Med Public Health* 2018; **5:** 4756-60.10.18203/2394-6040.ijcmph20184564

19 Malakar M, Choudhury M, Thinsin S, Bose RS — Investigation of an outbreak of varicella in a village of Goalpara district, India. *Int J Basic Clin Pharmacol* 2017; **6:** 93-6. 10.18203/2319-2003.ijbcp20164759

20 Kerketta AS, Dwibedi B, Subudhi P — Chickenpox Outbreak in a Tribal District Rayagada, Odisha, India: Warrants Need for Vaccination. *Poster Abstracts* 2019; OFID, **6 (Suppl 2):** S605.

21 Vadya SR, Tilavat SM — Varicella Outbreak in Children from Silvassa, Dadra and Nagar Haveli, India. *Indian Pediatrics* 2021; **58:** 483-4.

Original Article

Clinical Spectrum and Laboratory Parameters in Scrub Typhus in Children : Experience from a Tertiary Care Centre in West Bengal, India

Manik Mondal[1], Prakas Kumar Mandal[2], Rajarshi Basu[1], Tapan K Sinhamahapatra[3]

Background : Due to the vague symptoms of Scrub Typhus and the relative absence of eschar formation in Indian patients, clinical identification of Scrub Typhus from other acute febrile illnesses is exceedingly challenging. The goal of the current retrospective investigation was to incorporate the clinical and laboratory aspects to help with the diagnosis and treatment of Scrub Typhus in children.

Materials and Methods : Demographic profile, clinical features, laboratory parameters and treatment history were noted. Microsoft Office Excel 2007 was used to conduct the statistical analysis.

Results : Total 40 children with median age of five years were included; majority (85%) occurred in winter months. Mean Haemoglobin and Platelet counts were low at presentation but median Total Leukocyte Count was high. All patients treated with doxycycline and azithromycin either alone or in combination.

Conclusions : Poor/non-response of acute febrile illness to conventional antibiotic therapy must create high index of suspicion for Scrub Typhus. Prompt diagnosis of Scrub Typhus is helpful to reduce morbidity & mortality in children.

[*J Indian Med Assoc* 2023; **121(10):** 23-7]

Key words **: Children, Acute Febrile Illness, Scrub Typhus, Clinical Spectrum, Laboratory Parameters.**

One million individuals get sick from Scrub Typhus every year, which is a severe public health issue in the Asia-Pacific region that threatens one billion people worldwide[1]. An significant cause of Acute Undifferentiated Febrile Illness (AUFI) is the arthropod-borne Gram-negative obligate intracellular bacillus Orientia tsutsugamushi. An arthropod of the family can spread this sickness to people. In the past ten years, multiple outbreaks of the disease, known as Trombiculidae, have been documented from various regions of India[2-6]. Due to the lack of accurate diagnostic tests and the vague nature of symptoms, especially in the absence of distinctive eschar, misdiagnosis and underdiagnosis of this significant cause of AUFI are prevalent. All ages are affected and depending on how virulent the strain in question is, it can result in significant fatality rates of up to 50% of cases. Prognosis in O Tsutsugamushi infection can also be significantly influenced by the host factor and prompt treatment. A pathognomonic clinical symptom of Scrub Typhus is eschar. Eschars or other comparable lesions may be seen in many diseases, though, including anthrax, ulceroglandular tularaemia and other rickettsioses. Clinical evaluations and laboratory tests can be used to diagnose and differentiate from these entities. Indian Tick Typhus (ITT) caused by Rickettsia conorii causes eschar to develop ulcers and be covered in a brownish-black scab known as a "tache noire." Typically beginning at the ankles, lower legs, and wrists, maculopapular, petechial, or hemorrhagic eruptions traditionally involve the palms and soles and spread centripetally. Since Scrub Typhus doesn't have any distinct clinical manifestations, it's critical to educate clinicians about the clinical presentations, laboratory data and confirming diagnostic procedures. Previous reports of Scrub Typhus have come from a variety of locations in India, including the northern districts of West Bengal[7] and report of five cases solely from South Bengal in adults[6]. This is the first report of its sort and was conducted to explore the clinical profile and laboratory parameters in Scrub Typhus among children aged 2-11 years from

Editor's Comment :

- If acute febrile illness persists for more than one week duration in children of low socioeconomic class with overcrowding, we must search for scrub typhus.
- Several outbreaks have been reported from various parts of India in the last few decades & it is considered to be re-emerging disease. It is endemic in rural West Bengal especially during post monsoon & winter months.
- Non availability of reliable diagnostic test & non-specific symptoms especially poor detection of characteristic eschar led to misdiagnosis and under diagnosis of this important cause of acute undifferentiated febrile illness (AUFI).
- The present retrospective study aimed to integrate the clinical and laboratory features to aid the diagnosis and management of scrub typhus in children from West Bengal, India.
- A high index of suspicion could lead to early detection and treatment, which would greatly minimize death and morbidity.

Department of Pediatric Medicine, NRS Medical College and Hospital, Kolkata 700014

[1]MD (Pediatrics), Assistant Professor

[2]DM (Clinical Hematology), Associate Professor, Department of Hematology and Corresponding Author

[3]MD (Pediatrics), Professor & Head

Received on : 11/03/2022

Accepted on : 04/04/2022

the southern districts of West Bengal.

Materials and Methods

This was a retrospective cross-sectional study where we collected the data from our hospital records over a period of twenty-four months from July, 2018 to June, 2020. In all cases informed and written consent were taken from the parents and/or legal guardians as per institutional policy. All the patients admitted with fever in the Department of Paediatrics who were finally diagnosed with Scrub Typhus by serological tests (IgG & IgM) were included in the study. Demographic profile of patients including age, sex, area of residence, socio-economic status of the family and month of admission was studied. Clinical features, laboratory parameters, treatment history, course or events during stay in hospital and final outcome were evaluated in all these patients. Laboratory reports of tropical and other co-endemic diseases such as Dengue and Malaria tests were also reviewed carefully. Results of additional tests (where available) such as, Ultrasonography of abdomen, Chest X-ray, Electrocardiogram, Two-dimensional echocardiogram, Cerebrospinal fluid study and Computed Tomography of brain were also analysed. Treatment history of all the patients including those with complications was also noted. Medical documents of organ involvement, complications and treatment outcome were also analysed. Simple Statistical analysis was done with the help of Microsoft Office Excel 2007.

Results

During the course of the trial, 40 kids had Scrub Typhus diagnoses. The demographic and clinical profile of the patients at presentation was noted in Table 1. The following is an account of the distribution of cases according to :

Age, Sex & Residence (District) :

The patients under the present study had a median age of 5 years (range, 2-11 years); 19 (47.5%) patients were male. Majority (57.5%; n=23) were from Murshidabad district; next being from Nadia district.

Socio-economic Status :

In 29 (72.5%) cases the family belonged to lower Socio-economic Status (SES) as per revised Kupuswamy scale and 23 (57.5%) 9 patients reported overcrowding in the family. Month (of the year) of presentation: In our study majority cases (85%; n=34) occurred in the months from October to December with a peak in the month of November (40%; n=16).

Signs & Symptoms :

Fever was present in all cases, median duration of fever before admission was 8 days (range, 2-28 days) followed by drowsiness (50%), headache (45%), vomiting (45%) and body swelling (42.5%); in many cases overlapping of symptoms were there. Median temperature noted in patients was 100.1°F (range, 98-104°F), Mean Arterial Pressure (MAP) noted 78 mm of Hg (55-90); 9 (22.5%) patients admitted with features of shock. Hepatomegaly and Splenomegaly were present in 15 (37.5%) and 13 (32.5%) cases respectively. In two (5%) patients there was eschar formation.

Table 1 — *Demographic and clinical profile of the patients (n=40) at presentation*

Parameter Studied	Result
Age (years); median (range)	5 (2-11)
Sex : n (%) Male : female	19 (47.5%) : 21 (52.5%)
Month of presentation :	n (%)
March	1 (2.5%)
May	1 (2.5%)
June	2 (5%)
July	2 (5%)
September	5 (12.5%)
October	6 (15%)
November	16 (40%)
December	7 (17.5%)
Over-crowding; present, n (%)	23 (57.5%)
Socio economic status/Kupuswamy scale:	n (%)
Lower	29 (72.5%)
Upper Lower	11 (27.5%)
Symptoms :	
■ Fever present: n (%)	40 (100%)
■ Duration of fever before admission (days); median (range)	8 (2-28)
■ Headache: n (%)	18 (45%)
■ Chill : n (%)	6 (15%)
■ Muscle Pain: n (%)	9 (22.5%)
■ Body Swelling: n (%)	17 (42.5%)
■ Cough: n (%)	8 (20%)
■ Vomiting: n (%)	18 (45%)
■ Drowsiness: n (%)	20 (50%)
■ Bone pain: n (%)	2 (5%)
Signs :	
■ Temperature (°F); mean (range)	100.1 (98-104)
■ Respiration Rate (/min); median (range)	24 (18-40)
■ Pulse rate (counts/minute); median (range)	102 (82-134)
■ Systolic blood pressure (mm of Hg); median (range)	100 (80-118)
■ Diastolic blood pressure (mm of Hg); median (range)	66 (40-78)
■ Mean arterial pressure (mm of Hg); median (range)	78 (55-90)
■ SpO_2 (%); mean (range)	97 (92-99)
■ Redness of eyes; n (%)	4 (10%)
■ Oedema; n (%)	14 (35%)
■ Shock; n (%)	9 (22.5%)
■ Hepatomegaly; n (%)	15 (37.5%)
■ Splenomegaly; n (%)	13 (32.5%)
■ Eschar; n (%)	2 (5%)

Laboratory Parameters :

As shown in Table 2, mean hemoglobin and Platelet counts were low at presentation but median Total

Leukocyte Counts (TLC) and Absolute Neutrophil Counts (ANC) was high. The median values for serum creatinine, total bilirubin was normal but AST, ALT, ALP and LDH had shown higher values at diagnosis that had improved (within normal range) over time. Antibody tests (IgG & IgM) for Scrub Typhus was positive in all cases; in one case there was co-infection with Plasmodium vivax malaria (treated with antimalarial drug). The trend in change of different blood counts is shown in Fig 1.

Antibiotic Therapy :

Twenty (50%) patients and 4 (10%) patients were treated with doxycycline and azithromycin alone respectively and 15 (37.5%) cases were treated with combination of both antibiotics (Table 3). In one case (2.5%), the patient (a 3years 2months old girl) who presented on day 23 of fever with features of sepsis, meningitis, left abducens nerve palsy and myocarditis; in addition to doxycycline and azithromycin, inj Meropenem and vancomycin was added to therapy.

Organ Involvement and Complications:

The different organ involvement and complications are presented in Fig 2; in one case patient required ventilator support and the patient survived. The patient who developed features of sepsis, meningitis, left abducens nerve palsy and myocarditis; subsequently developed multi-organ dysfunction and succumbed on day 26.

Discussion

In the Indian subcontinent, rickettsial illnesses are reportedly resurfacing with a more diverse geographic distribution[8-10].

Despite being the most widespread rickettsial illness in India, Scrub Typhus is one of the country's most overlooked zoonoses of public health significance[11]. Scrub Typhus was very common during the Second World War, especially among the soldiers in the far East. Scrub Typhus prevalence has dramatically grown recently and eastern and southern Asia is now regarded regions where it is re-emerging.

Worldwide, one billion people are at risk and around one million cases are reported every year[11]. This is endemic to the "tsutsugamushi triangle," a massive 13 million km2 triangular region in eastern Asia that includes India, Pakistan, and Afghanistan. It extends from Japan in the East. The impacted regions of India are a sizable portion of the North (Kashmir, Himachal Pradesh), East (Assam, Sikkim, and Darjeeling of West Bengal) and a small portion of the South (Eastern and Western Ghats). Recent review analysis shows that this disease is no longer

Table 2 — *Laboratory parameters of the children included in the study (n=40)*

	Day 0	Day 3	Day 7
Blood counts	-	-	-
Hemoglobin (gm/dl); mean (range)	9.4 (7.2-11.6)	9.3 (6.0-11.0)	9.7 (6.6-12.1)
Total leukocyte count (cells/µL); median (range)	11,700 (1,700-26,700)	9, 600 (2,400 -18,500)	7,550 (3,300-22,100)
Absolute neutrophil count (cells/µL); median (range)	5,780 (680-15,219)	4,796 (1,200 - 12,480)	3,783 (825-10,395)
Neutrophil (%); median (range)	57 (20-85)	50 (25-78)	48 (22-78)
Lymphocyte (%); median (range)	38 (11 - 73)	43 (20-71)	49 (18-73)
Eosinophil (%); median (range)	2 (0-5)	1 (0-7)	1 (0-8)
Monocyte (%); median (range)	2 (0-7)	4 (1-7)	3 (0-9)
Platelet count (cells/µL); median (range)	120,000 (30,000-530,000)	150,000 (40,000-800,000)	225,000 (90,000-600,000)
Blood Biochemistry	-	-	-
Urea (mg/dl); median (range)	24 (15-71)	21 (15-60)	21 (13-79)
Creatinine (mg/dl); median (range)	0.7 (0.4-1.0)	0.6 (0.3-0.8)	0.6 (0.3-2.4)
Total serum bilirubin(mg/dl); median (range)	0.5 (0.3-5.1)	0.6 (0.3-2.1)	0.6 (0.3-1.6)
Conjugated bilirubin(mg/dl); median (range)	0.15 (0.1-1.4)	0.2 (0.1-1.0)	0.2 (0.1-0.8)
Total protein (gm/dl); median (range)	6.0 (4.4-7.9)	6.1 (3.9-7.6)	6.4 (4.6-7.9)
Serum albumin (gm/dl); median (range)	3.0 (2.0-4.0)	3.15 (1.7-4.5)	3.35 (2.2-4.2)
AST (IU/L); median (range)	100.5 (19-754)	75.5 (20-540)	62 (21-320)
ALT (IU/L); median (range)	58.5 (15-391)	50 (12-194)	45.5 (15-156)
ALP (IU/L); median (range)	164.5 (33- 770)	134 (56-603)	118 (40-300)
LDH (IU/L); median (range)	450 (106-1883)	335 (48-1580)	340 (48-1210)
Fasting plasma glucose (mg/dl); median (range)	106 (50-118)	75.5 (56-100)	82.5 (62- 122)
Serum sodium (meqv/L); median (range)	131 (125-143)	135 (124-143)	137 (128-145)
Serum Potasium (meqv/L); median (range)	4.45 (2.6 – 6.2)	4.2 (2.7-5.2)	3.8 (3.3-5.0)
CSF examination (done in 10 cases)	-		
Cell count(cells/µL); median (range)	10 (3-35)		
Neutrophils (cells/µL); median (range)	5.5 (0-12)		
Lymphocytes (cells/µL); median (range)	5.5 (0-23)		
Sugar (mg/dl); median (range)	55 (45-69)		
Protein (mg/dl); median (range)	35 (10-98)		
Serology	-		
Malaria Parasite Dual Antigen (MPDA)	**Non-Reactive- 39**		**P. vivax- 1 case**
Dengue (NS1Ag)	Non-Reactive- 36		Reactive- 4
Dengue (IgM)	Non Reactive- 40		Reactive-0
Dengue (IgG)	Non Reactive- 40		Reactive-0
Scrub typhus (IgG)	Non Reactive- 0		Reactive- 40
Scrub typhus (IgM)	Non Reactive- 0		Reactive- 40

restricted to the 'Tsutsugamushi Triangle'; can be caused by Orientiae other than Orientia tsutsugamushi[12]. Scrub Typhus has been previously reported from the northern districts of West Bengal by Mallick SK, *et al*[7] and Sharma PK, *et al*[13]. But, there is scarcity of data from the central, western and southern districts of West Bengal except the published report of five cases of Scrub Tuphus from South Bengal that also mostly in adults[6].

Absence of a documented report does not imply total absence of the disease; rather, it may indicate a lack of diagnosis and reporting rather than the disease's actual absence in the region. Eschar is known to develop in 7% to 80% of Scrub Typhus cases[14]. Absence of eschar increases the risk of misdiagnosis; presence of eschar in hidden body areas may impair detection; dark skin color is also known to make it more difficult to identify. The indigenous people of endemic locations may less frequently acquire characteristic eschar or even the other classical skin rashes and typically manifest with less severe sickness, which is more significant given that eschar is believed to be rare in South-East Asian patients.[15]

Scrub Typhus patients with light-skinned South Asians and Caucasians are more likely to have diagnostic eschar present than those with dark skin tones[14]. In addition, doxycycline may have been used as an experimental treatment in many cases without a confirmed diagnosis. Due to these facts and the extremely low level of suspicion around them, there may be no reported cases.In tropical nations like India; acute undifferentiated fevers are quite common during the monsoon and post-monsoon seasons because these conditions are ideal for mosquito breeding and mite growth. Disease transmission is aided by a high incidence of infectious vectors, increasing human-vector contact, high temperatures, high humidity, persistent rains and lush vegetation growth.The varied

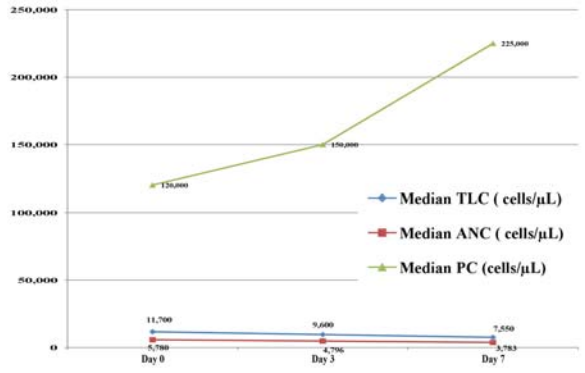


Fig 1 — Trends in change of Total Leukocyte Count (TLC), Absolute Neutrophil Count (ANC) and Platelet Count (PC) over time (n=40)

Table 3 — *Treatment History of the patients (n=40) included in the study*

ANTIBIOTIC USED	n (%)
Azithromycin alone	4 (10%)
Doxycycline alone	20 (50%)
Azithromycin + Doxycycline	15 (37.5%)
Azithromycin + Doxycycline +meropenem+vancomycin	1 (2.5%)

etiological agents and similarity in clinical presentation further impede accurate diagnosis and effective management of AUFI. In various nations, the prevalence of Scrub Typhus ranges from 0-8% to 60%[15]. Sivarajan S, *et al*[16] from North East India reported the majority of cases in the age range of 20 to 50 years without any gender predominance, while two separate investigations from South India found a little male preponderance[17-18]. In the current analysis, the month of November saw the highest incidence of Scrub Typhus, which then began to fall in the months that followed. Scrub-typhus cases are most prevalent in South India during the cooler months of August through January, whereas in Southeast Asia, cases are most prevalent from July through November[19]. The most frequent clinical manifestation was fever, which affected 100% of participants in a number of investigations, according to[4,16-18,20-21]. A high index of suspicion for Scrub Typhus is required for rapid identification, treatment and consequent reduction in mortality in such individuals since complications are more likely to develop after the first week of illness. Scrub Typhus patients who are delayed in receiving treatment have higher morbidity and fatality rates[22]. The present study documented eschar in 5.0% patients compared 7% to 97% in various studies[23]. There was only one (2.5%) death in the present study. This may be due to doctors' better awareness of the various clinical manifestations of Scrub Typhus, as well as to earlier detection and treatment. Delayed treatment in patients with Scrub Typhus increases morbidity and mortality[24-25]. In a

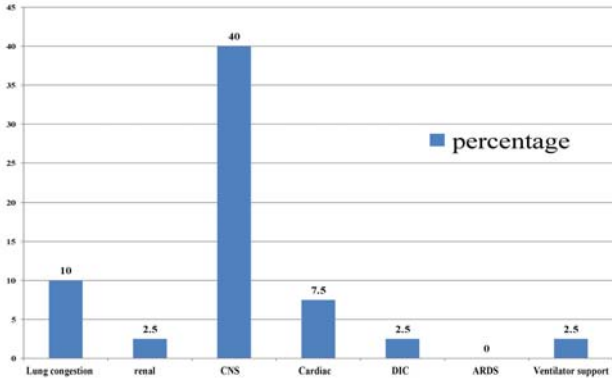


Fig 2 — Details of different organ involvement and complications in children under the study (n=40)

published research on the risk variables for Acute Respiratory Distress Syndrome (ARDS) in Scrub Typhus patients found a substantial correlation between ARDS and extended untreated fever[26]. The majority of AUFI patients in underdeveloped nations arrive in Tertiary Care Hospitals 7 to 10 days into their illness, by which point IgM antibody levels would be detectable. In conclusion, any undifferentiated fever lasting longer than one week that does not improve after being treated with typical empirical antibiotics warrants a clinical and diagnostic workup for Scrub Typhus. A combination of clinical characteristics, laboratory data and a serological test would be helpful in the early commencement of particular medication in patients with Scrub Typhus because findings of confirmatory testing are not always immediately available. The current study is eye-opening and suggests that there may be many other undiscovered instances existing in these areas (districts) of West Bengal. It also emphasizes the need for enhanced sensitivity among doctors to suspect Scrub Typhus at an early stage.

Conclusion

Scrub Typhus is one of the important causes of acute febrile illness of more than one week duration in children of low Socio-economic class with overcrowding. It is endemic in rural West Bengal especially during post-monsoon & winter.

Source of Funding : None

Conflict of interest : No Conflicts of Interest declared by any author

References

1 Kelly DJ, Forest PA, Ching WM, Richards AL — Scrub typhus: the geographic distribution of phenotypic and genotypic variants of Orientia tsutsugamushi. *Clin Infect Dis* 2009; **48:** S203-230.
2 Varghese G, Abraham O, Mathai D, Thomas K, Aaron R, Kavitha ML, *et al* — Scrub typhus among hospitalized patients with febrile illness in South India: magnitude and clinical predictors. *J Infect* 2006; **52:** 56-60.
3 Sinha P, Gupta S, Dawra R, Rijhawan P — Recent outbreak of scrub typhus in North Western part of India. *Indian J Med Microbiol* 2014; **32:** 247-50.
4 Dass R, Deka NM, Duwarah SG, Barman H, Hoque R, Mili D, *et al* — Characteristics of paediatric scrub typhus during an outbreak in the North Eastern region of India: peculiarities in clinical presentation, laboratory findings and complications. *Indian J Pediatr* 2011; **78:** 1365-70.
5 Chrispal A, Boorugu H, Gopinath KG, Prakash JA, Chandy S, Abraham OC, *et al* — Scrub typhus: an unrecognized threat in South India—clinical profile and predictors of mortality. *Trop Doct* 2010; **40:** 129-33.
6 Khan SA, Dutta P, Khan AM, Topno R, Borah J, Chowdhury P, *et al* — Re-emergence of scrub typhus in northeast India. *Int J Infect Dis* 2012; **16(12):** e889-890.
7 Mallick SK, Hazra S, Nandi T, Sarkar A — Scrub typhus: a hospital-based study in the northern districts of West Bengal, India. *Int J Res Med Sci* 2019; **7:** 2403-7.
8 Ahmad S, Srivastava S, Verma SK, Puri P, Shirazi N — Scrub typhus in Uttarakhand, India: A common rickettsial disease in an uncommon geographical region. *Trop Doct* 2010; **40:** 188-90.
9 Chaudhry D, Garg A, Singh I, Tandon C, Saini R — Rickettsial diseases in Haryana: Not an uncommon entity. *J Assoc Physicians India* 2009; **57:** 334-7.
10 Razak A, Sathyanarayanan V, Prabhu M, Sangar M, Balasubramanian R — Scrub typhus in Southern India: Are we doing enough? *Trop Doct* 2010; **40:** 149-51.
11 John TJ, Dandona L, Sharma VP, Kakkar M — Continuing challenge of infectious diseases in India. *Lancet* 2011; **377:** 252-69.
12 Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Curr Opin Infect Dis* 2003; **16:** 429-36.
13 Sharma PK, Ramakrishnan R, Hutin YJ — Scrub typhus in Darjeeling, India: opportunities for simple, practical prevention measures. *Trans R Soc Trop Med Hyg* 2009; **103(11):** 1153-8. doi:10.1016/j.trstmh.2009.02.006
14 Kundavaram AP, Jonathan AJ, Nathaniel SD, Varghese GM — Eschar in scrub typhus: A valuable clue to the diagnosis. *J Postgrad Med* 2013; **59:** 177-8.
15 Taylar AC, Hill J, Kelly DJ, Davis DR, Lewis GE Jr — A serological survey of scrub, tick, and endemic typhus in Sabah, East Malaysia. *Southeast Asian J Trop Med Public Health* 1986; **17:** 613-9.
16 Sivarajan S, Shivalli S, Bhuyan D, Mawlong M, Barman R — Clinical and paraclinical profile, and predictors of outcome in 90 cases of scrub typhus, Meghalaya, India. *Infect Dis Poverty* 2016; **5:** 91.
17 Anitharaj V, Stephen S, Pradeep J, Park S, Kim SH, Kim YJ, *et al* — Serological diagnosis of acute scrub typhus in Southern India: evaluation of InBios Scrub typhus detect IgM rapid test and comparison with other serological tests. *J Clin Diagn Res* 2016; **10:** DC07- DC10.
18 Ramyasree A, Kalawat U, Rani ND, Chaudhury A — Seroprevalence of Scrub typhus at a tertiary care hospital in Andhra Pradesh. *Indian J Med Microbiol* 2015; **33:** 68-72.
19 Subbalaxmi MV, Madisetty MK, Prasad AK, Teja VD, Swaroopa K, Chandra N, *et al* — Outbreak of scrub typhus in Andhra Pradesh—experience at a tertiary care hospital. *J Assoc Physicians India* 2014; **62:** 490-6.
20 Aung AK, Spelman DW, Murray RJ, Graves S — Rickettsialinfectionsin Southeast Asia: implications for local populace and febrile returned travelers. *Am J Trop Med Hyg* 2014; **91:** 451-60.
21 Palanivel S, Nedunchelian K, Poovazhagi V, Raghunadan R, Ramachandran P. Clinical profile of scrub typhus in children. *Indian J Pediatr* 2012; **79:** 1459-62.
22 Kumar M, Krishnamurthy S, Delhi Kumar CG, Narayanan P, Biswal N, Srinivasan S — Scrub typhus in children at a tertiary hospital in southern India: Clinical profile and complications. *J Infect Public Health* 2012; **5:** 82-8.
23 Kim DM, Won KJ, Park CY, Yu KD, Kim HS, Yang TY, *et al* — Distribution of eschars on the body of scrub typhus patients: a prospective study. *Am J Trop Med Hyg* 2007; **76:** 806-9.
24 Paris DH, Shelite TR, Day NP, Walker DH — Unresolved problems related to scrub typhus: A seriously neglected life-threatening disease. *Am J Trop Med Hyg* 2013; **89:** 301-7.
25 Yasunaga H, Horiguchi H, Kuwabara K, Hashimoto H, Matsuda S — Delay in tetracycline treatment increases the risk of complications in Tsutsugamushi disease: data from the Japanese Diagnosis Procedure Combination database. *Intern Med* 2011; **50:** 37-42.
26 Venkategowda PM, Rao SM, Mutkule DP, Rao MV, Taggu AN— Scrub typhus: Clinical spectrum and outcome. *Indian J Crit Care Med* 2015; **19:** 208-13.

Original Article

Role of D-dimer and CA-125 in the Detection of Ovarian Malignancy

Roshini Shekhar[1], Ganga S Pilli[2], Ramadevi V Wani[3], Mrityunjay C Metgud[4]

Aims and Objectives : The aim of our study was to analyze the role of D-dimer and CA-125 in the pre-operative diagnosis of ovarian malignancy and understand its significance.

Materials and Methods : The present prospective study was carried out on patients with ovarian tumors for a period of one year at the department of pathology. A total of 40 cases were studied. Demographic data, a thorough history and clinical findings were recorded in a pre-designed format. D-dimer and CA-125 levels were estimated in the blood samples. Histopathological study was carried out on the operated ovarian neoplasms in all the patients. D-dimer value <0.3 mg/L and CA 125 value ≤35 U/ml were considered normal. Statistical analysis was done using the Chi-square test and student's t-test. A probability value 'p' of ≤0.05 was considered statistically significant.

Results : Out of 40 patients, 24 patients had benign tumours and 16 had malignant tumours. As regards the prediction of malignancy D-dimer showed a sensitivity of 81.25% and specificity of 62.5% and CA-125 showed a sensitivity of 50% and specificity of 87.5%.The association between D-dimer and CA-125 showed a 'p' value of 0.036 thus suggesting that D-dimer is useful in diagnosing ovarian cancer. Compared to CA125, D-dimer was found to be a more sensitive predictor of ovarian malignancy.

Conclusion : Sensitivity for detecting ovarian malignancy was better with D-dimer than with CA-125. D-dimer levels also co-related with the advancing stage of ovarian malignancy. Hence, this marker may be used as a diagnostic as well as a prognostic marker in ovarian malignancy.

[*J Indian Med Assoc* 2023; **121(10):** 28-31]

Key words **: Ovarian Tumours, Ovarian Malignancy, Ovarian Carcinoma, D-dimer, CA-125.**

Ovarian malignancy is the eighth most common cancer among women worldwide[1] and third most common among Indian women[2] accounting for 6.7% of all cancers. The majority of ovarian cancers (90%) are derived from epithelial cells and cancers from germ cells and sex cord-stromal cells comprise the reminder[3]. If diagnosed and treated in stage I the survival is more than 90%. But most patients are only diagnosed in the advanced stage which is associated with poor survival (5-year survival of 27% for stage III and 17% for stage IV)[4]. Thus, to improve survival, it is important that ovarian canceris detected in the early stage. It is difficult to diagnose ovarian cancer in its early stages, as it may be asymptomatic or present with vague complaints like pain abdomen, bloating, loss of appetite etc, which can be confused with other common benign conditions. Hence, several biomarkers are used in an attempt to distinguish between benign and malignant epithelial ovarian tumours and to detect ovarian malignancy in the early stage.

Editor's Comment :

- Our study showed sensitivity for detecting ovarian malignancy to be better with D-dimer than with CA-125. However, larger studies are required for confirmation.
- D-dimer levels can be used as a prognostic marker as the levels co-related with the advancing stage of ovarian cancer.

Aims and Objectives

CA-125 is extensively used as a tumour marker for the detection of epithelial ovarian cancer. However, it is also elevated in certain physiologic conditions like menstruation and pregnancy and certain benign conditions like fibroids, endometriosis, pelvic inflammatory diseases, etc leading to false positive results[5]. It is raised in just 50% of Stage-1 epithelial ovarian cancer and 75-90% of patients with advanced disease[6]. Therefore, it is not a suitable biomarker for the early detection of ovarian epithelial cancer. The search for reliable tumour markers continues. Of late the role of hemostatic markers is being studied. Tumour cells secrete procoagulant/ fibrinolytic substances in addition to other factors resulting in a state of

[1]MD, Consultant Pathologist, Department of Pathology, Manipal Hospital, Bangalore, Karnataka 560017

[2]MD, Professor and Head, Department of Pathology, KLE JGMM Medical College, Hubballi, Karnataka 580028 and Corresponding Author

[3]MRCOG, Consultant, Department of Obstetrics & Gynaecology, KLE's Dr Prabhakar Kore Hospital & Medical Research Centre, Karnataka 590010

[4]MD, Professor, Department of Obstetrics & Gynaecology, KLE's Dr Prabhakar Kore Hospital & Medical Research Centre, Karnataka 590010

Received on : 27/12/2022
Accepted on : 25/06/2023

hypercoagulation and fibrinolysis in patients with cancer, especially in the advanced stage. D-dimer, a signal of activated coagulation and an end product of fibrinogen is elevated in many cancers[7]. Few studies have found that the D-dimer level is increased significantly in patients with ovarian cancer[8,9]. To explore further we took up this study. The aim of our study was to evaluate the role of D-dimer and CA-125 in the pre-operative diagnosis of ovarian cancer and understand its clinical significance.

Materials and Methods

The present study was carried out on patients with ovarian tumours for a period of one year in the Department of pathology of a reputed Medical College with its attached Tertiary Care Hospital. All pre-operative patients presenting with an ovarian mass detected by clinical examination and /or Ultrasonography were included in the study. The patients with pre-existing liver disease, inherited bleeding disorders, on anticoagulant therapy or oral contraceptives were excluded from the study.

A total of 40 cases were studied. Ethical clearance for the study was obtained from Institutional Ethics Committee on Human subjects Research. Written informed consent was obtained from the patients. Demographic data such as age, marital status, a thorough history of presenting complaints and significant past history were recorded in a predesigned and pre-tested proforma.

Blood samples for D-dimer and CA-125 were tested and a histopathological study of the ovarian tumour was done for all the patients. Plasma D-dimer estimation was done using Nyco Card assay. In the presence of D-dimer levels above 0.1 mg/L in the sample, the membrane appears reddish with a colour intensity proportional to the D-dimer concentration. The colour intensity was evaluated using Nyco Card reader. Blood samples for quantitative estimation of serum CA-125 were done using radioimmunoassay. Values <35U/ml were considered normal. Ovarian specimens in 10% formalin were grossly examined and findings were noted. The laterality, size, consistency, cystic and solid areas, necrosis, haemorrhage and papillae were evaluated and noted. Histopathology findings from the cyst wall, solid areas, papillae and any other suspicious appearing areas were studied.

Statistical analysis for correlation for categorical data was done by Chi-square test and correlation of continuous data was done by student's 't' test. A probability value 'p' of ≤ 0.05 was considered statistically significant.

Observations

The present one-year hospital-based prospective study was carried out on 40 patients with ovarian neoplasms detected pre-operatively by clinical examination/ultrasonography and confirmed by histopathology.

The age of patients (Table1) in our study ranged from 13-74 years. The mean age of presentation for malignant cases was 43.1±16.25 years and the most prevalent age group for ovarian carcinoma was >50 years accounting for 7 cases (17.5%). This was followed in descending order by 31-50 years with 6 cases (15%) and 0-15 years age group with 2 cases (10%) respectively and 16-30 year age group with 1 case (2.5%). The most common age group for benign tumours was 16-30 years (25%). The youngest patient with a malignant tumour was aged 13 years (mixed germ cell tumour) while the oldest was 74 years (mucinous cystadenocarcinoma).

D-dimer (Table 2) was raised in 22 patients (55%) and was normal in 18 (45%) patients. D-dimer was raised in 13 out of 16 patients with malignant tumours ie, 81.25% and was raised in 37.5% of patients with benign tumours. As regards the prediction of malignancy, the sensitivity was 81.25% and specificity was 62.5%. The positive predictive value was 59.09% whilst the negative predictive value was 83.33%.

CA-125 (Table 3) was raised in 11 patients (27.5%) and was normal in 29 (72.5%) patients. CA-125 was raised in 8 out of 16 patients with malignant tumours, ie, 50% and was raised in 12.5% of patients with benign tumours. Sensitivity was 50% and specificity was

Table 1 — *Age distribution of the study patients*

Age group (Years)	Distribution (n=40)			
	Benign	Malignant	Total	Percent
0-15	0	2	2	5
16-30	10	1	11	27.5
31-50	7	6	13	32.5
> 50	7	7	14	35
Total	24	16	40	100

Table 2 — *D-dimer levels in the study patients*

D-dimer levels	Distribution (n=40)			
	Malignant	Benign	Total	Percent
Raised (>0.3)	13	9	22	55
Normal (0.1-0.3)	3	15	18	45
Total	16	24	40	100

Table 3 — *CA-125 levels in the study patients*

CA-125 Level	Distribution (n=40)			
	Malignant	Benign	Total	Percent
Raised	8	3	11	27.5
Normal	8	21	29	72.5
Total	16	24	40	100

87.5%. The positive predictive value was 72.73% while the negative predictive value was 72.41%.

Therefore, an association exists between D-dimer levels and CA-125 levels (Table 4).

Out of 40 patients, 16 had malignant tumours and 24 had benign tumours. The most common benign tumour was serous cystadenoma, 11 patients (27.5%). Surface epithelial tumours were the most common group comprising 31 patients (77.5%). The most common malignant tumour was papillary serous cyst adenocarcinoma accounting for 6 patients (15%). 4 patients (10%) had germ cell tumours while 3 patients (7.5%) had stromal tumours and 2 patients (5%) had metastatic tumours (Table 5).

Discussion

Worldwide, in the year 2020, nearly 3,14,000 women were diagnosed with ovarian cancer and over 2,07,000 died from this disease[1]. In India, the age-adjusted incidence varies from 0.9- 8.4 per 100,000 women in various population-based registries[10]. Ovarian cancer has the worst prognosis among all the gynaecological malignancies. There is a continued search for tumour markers to detect ovarian cancer in the early stage, as it has a very good prognosis if detected in the early stages.

Table 4 — *D-dimer and CA-125 association*

		CA-125 Levels		
		Raised	Normal	Total
D-dimer Levels	Raised	9	13	22
	Normal	2	16	18
	Total	11	29	40

Kappa = 0.282 and p value= 0.036

Table 5 — *Distribution of the histological types of primary ovarian tumour*

Type	Number	Percentage
Benign (24)		
Serous cystadenoma	11	27.5
Mucinous cystadenoma	6	15
Mature teratoma	2	5
Granulosa cell tumour	2	5
Adenofibroma	1	2.5
Brenner's tumour	1	2.5
Mixed sero-mucinous adenoma	1	2.5
Malignant (16)		
Papillary serous cyst adenocarcinoma	6	15
Mucinous cystadenocarcinoma	2	5
Clear cell carcinoma	1	2.5
Endometrioid carcinoma	1	2.5
Transitional cell carcinoma	1	2.5
Malignant mixed Mullerian tumour	1	2.5
Dysgerminoma+yolk sac tumour	2	5
Metastatic adenocarcinoma	2	5

Ultrasonography and estimation of CA- 125 are the standard procedures to evaluate ovarian tumours for malignancy. However, CA-125 shows positive results in various benign gynaecological conditions and other cancers. It has low sensitivity and low specificity when used as a marker for the diagnosis of ovarian carcinoma. Al Musalhi K, *et al* in their study showed that CA-125 was raised in 69% of patients with malignant ovarian tumours[11]. Our study too showed a poor sensitivity of 50% in the detection of ovarian carcinoma.

A study by Worasthsin P and Narkwichian A[8] showed that the measurement of D-dimer and CA-125 were beneficial in differentiating benign from malignant ovarian tumours. In their study, D-dimer was better than CA-125, in differentiating benign from malignant ovarian tumours. Recently the meta-analysis by Wu J, *et al*[12] concluded that the plasma D-dimer level was higher in ovarian cancer patients compared to benign controls. Our study showed similar results to these studies. D- dimer was raised in 81.25% (13 out of 16 patients) of patients with malignant tumours, compared to the raised levels in only 37.5% of patients with benign tumours. In 3 patients with false positive D-dimer results, though there was no ovarian malignancy and they had a benign ovarian tumour, the raised D-dimer level directed to diagnose coexisting other malignancies (2 soft tissue sarcomas and 1 case of Fallopian tube adenocarcinoma).

In the present study, the association (kappa value) between D-dimer and CA-125 was 0.282 and the p-value was 0.036. Compared to CA-125, D-dimer is therefore a more sensitive predictor of ovarian malignancy. Similar findings were noted by Sakurai, *et al*. They also showed that D-dimer values are more sensitive in predicting advanced stages and prognosis than CA-125[13]. Several other studies[8, 14] also showed that the D-dimer levels positively correlated with FIGO classification. D-dimer is even more increased in patients with advanced ovarian cancer and metastatic malignant disease[11]. We had four patients with Stage IV ovarian carcinoma. These patients showed the highest D-Dimer levels with a mean value of 0.525 U/ml. Thus, our study results were concordant with these results.

Conclusion

Sensitivity for detecting ovarian malignancy is better with D-dimer than with CA-125. D-dimer levels also co-related with the advancing stage of ovarian cancer. Hence, this marker may be used as a diagnostic as well as a prognostic marker in ovarian malignancy.

References

1 Hyuna Sung, Jacques Ferlay, Rebecca L. Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, Freddie Bray Global Cancer Statistics 2020; GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries CA CANCER J CLIN 2021; **71:** 209-49.

2 https://gco.iarc.fr>data>356-india-fact-sheets

3 Torre LA, Trabert B, DeSantis CE — Ovarian cancer statistics. CA: A Cancer Journal for Clinicians 2018; **68:** 284-96.

4 Cancer Research UK — Ovarian cancer survival statistics. https://www.cancerresearchuk.orghealth-professional/cancer-statistics/statistics-by-cancer-type/ovarian -cancer/survival# heading-Three (2018)

5 Miralles C, Orea M, Espana P — Cancer antigen 125 associated with multiple benign and malignant pathologies. *Ann Surg Oncol* 2003; **10:** 150-4.

6 Moss EL, Hollingworth J, Reynolds TM — The role of CA 125 in clinical practice. *J Clin Pathol* 2005; **58(3):** 308-12.

7 Siddiqui N A, Malik M, Wijeratne Fernando R — D-Dimer: a Potential Solutions to Problems of Cancer Screening, Surveillance, and Prognosis Assessment. *Cureus* 2021; **13(5):** e15064.

8 Worasethsin P, Narkwichean A — D-dimer as a tumour marker in the pre-operative assessment of adnexal masses. *J Med Assoc Thai* 2013; **96(11):** 1395-400.

9 Wu X, Xue X, Tang J, Cheng X, Tian W, Jiang R, *et al* — Evaluation of risk factors for venous thromboembolism in Chinese women with epithelial ovarian cancer. *Int J Gynecol Cancer* 2013; **23(1):** 65-72.

10 Murthy NS, Shalini S, Suman G — Changing trends in incidence of ovarian cancer- the Indian scenario. *Asian PAC J Cancer Prev* 2009; **10:** 1025-30.

11 Al-Musalhi k, Al-Kindi M, Ramadhan F, Al-Rawahi T, Al-Hatali K, Mula-Abed WA — Validity of cancer antigen -125(CA-125) and risk of malignancy index (RMA) in the diagnosis of ovarian cancer. *Oman Med J* 2015; **30(6):** 428-34.

12 Wu J, Fu Z, Liu G, Xu P, Xu J, Jia X — Clinical significance of plasma D-dimer in ovarian cancer: A meta-analysis. *Medicine (Baltimore)* 2017; **96(25):** e7062.

13 Sakurai M, Satoh T, Matsumoto K, Michikami H, Nakamura Y, Nakao S, *et al* — High pretreatment plasma D-dimer Levels areassociated with Poor Prognosis in Patients with Ovarian Cancer Independently of Venous Thromboembolismand Tumour Extension. *Int J Gynecol Cancer* 2015; **25(4):** 593-8.

14 Vahid Dastjerdi M, Ahmari S, Alipour S, Tehranian A — The comparison of plasma D-dimer levels in benign and malignant tumours of cervix,ovaryand uterus. *Int J Hematol Oncol Stem Cell Res* 2015; **9(3):** 107-11.

Original Article

Dermatophytosis in paediatric population : A study on clinico-epidemiological and mycological profile from eastern India

Niharika Ranjan Lal[1], Nabanita Das[2], Roumi Ghosh[3]

Background : Of late, superficial dermatophyte infections has been witnessing an alarming change among paediatric population. Not only is there a rising prevalence but also children are now presenting with involvement of glabrous skin and extensive lesions.

Aims and Objectives : To study the epidemiological and clinic-mycological profile of tinea infection in the paediatric population.

Materials and Methods : A Prospective Observational study was done on all cases up to 15 years of age who presented with a clinical picture characteristic/suspicious of tinea and were studied for pattern of infection and environmental associations.

Result : The prevalence rate of Paediatric Dermatophyte infection was found to be 19.79% and was mostly seen in the 11-15 years age group with a male-to-female ratio of 1.73:1. About 62.09% of children belonged to rural background and 64.70% were from a low socio-economic strata. Almost 56.2% of children reported contact with an affected family member, 29.41% had a habit of pond bathing and 69.9% shared towel with other members of family. Nearly 77.1% of children had sought treatment previously before presenting to us of which majority (28.8%) had used over the counter medications from a pharmacy. Around 61.02% children had applied steroids. Clinically, the most common presentation was tinea corporis (84.96%) and 56.86% of children presented with extensive body involvement. Direct microscopy and fungal culture were positive in 67.32% and 44.44% cases respectively. The most common species isolated was *Trichophyton mentagrophytes* (51.47%).

Conclusion: Paediatric superficial dermatophytosis is now presenting more in adult pattern. Awareness about personal hygiene, avoidance of self-medication and treatment compliance can help reduce the disease burden.

[*J Indian Med Assoc* 2023; **121(10):** 32-6]

Key words **: Superficial Dermatophytosis, Paediatric, Tinea.**

Skin of the Infantile and Paediatric age group is prone to infections because of increased predilection for minor trauma and childhood allergies[1]. Fungal infections of the skin and scalp represent a relatively common problem, especially in the tropical and subtropical regions of the World, where warm and humid climate provides a favourable environment for the growth of fungus[2]. Dermatophytosis is the most common type of cutaneous fungal infection seen in humans in developing countries due to increasing use of immuno-suppressive drugs and increasing prevalence of chronic diseases associated with impaired immunity, primarily diabetes[3]. Children are particularly susceptible to Dermatophyte infections because of their poor personal hygiene and habits.

[1]MD, Assistant Professor, Department of Dermatology, ESI-PGIMSR & ESI Medical College & Hospital, Joka, West Bengal 700058 and Corresponding Author

[2]MD, Consultant Dermatologist, Durgapur Steel Plant Hospital, Durgapur, West Bengal 713203

[3]MD, DNB, Assistant Professor, Department of Microbiology, ESI-PGIMSR & ESI Medical College & Hospital, Joka, West Bengal 700058

Received on : 23/04/2023

Accepted on : 28/04/2023

Editor's Comment :

- Parents must be educated about personal hygiene amongst all members which includes avoiding pond bathing, keeping separate towel and soap, not wearing damp clothes, avoiding synthetic garments, for long and keeping the skin folds dry.
- Steroid misuse, treatment non-compliance and incomplete prescription were important factors for high infection rates among children emerged as leading factors for long duration of infection. Proper awareness of the parents regarding health education, avoidance of self-medication or treatment by unqualified personnel is highly needed to control the disease burden in the society.
- Lifestyle modification and weight reduction should be advised for obese children.

Dermatophytosis has been extensively studied with respect to the socio-demographic, mycological, and clinical profile of the disease. Many atypical clinical presentations have also been reported which include erythema-multiforme like, seborrheic- dermatitis like, lupus-erythematosus like, dermatitis-herpetiformis like, and psoriasis- like to name a few[4]. However, most of the studies till date have been done on adult population. Indian studies on paediatric population are very few. The aim of the study was to assess the clinico-

epidemiological and mycological profile of tinea in children and to assess the knowledge regarding use of over the counter drugs, steroid abuse among others.

Materials and Methods

The present observational study was undertaken in the Department of Dermatology of a Tertiary Care Hospital in Eastern India between July 2021 to January 2022. All patients up to 15 years of age who presented to our Outpatient Department during the study duration with a clinical picture that was characteristic or suggestive of tinea were included in the study. Institutional Ethics Committee clearance and parental consent (for patients <12 years of age) for participation in the study were obtained. All patients who were once enrolled in the study were excluded during subsequent follow-up visits.

At the time of enrolment, a detailed pre-designed proforma was recorded for each patient in which the patient's socio-demographic data including age, sex, area of residence (urban/rural), housing conditions with respect to overcrowding, and socio-economic status were noted. Clinical data including duration of disease, past history of tinea, treatment history, pre-existing Co-morbidities and family history of similar disease was also recorded.

Clinical features like the pattern of tinea and site/s of involvement was recorded and classified as follows: a single lesion was classified as "single lesion - localized disease"; multiple lesions in a single anatomical site or 2 contiguous anatomical sites was classified as "multiple lesions - localized disease"; involvement of more than one non-contiguous anatomical sites or more than two contiguous anatomical sites was classified as "extensive disease". Clinical photographs of the site bearing the lesions were taken after taking consent of parents/ child.

Samples of skin scraping/ hair filaments / and nail clippings were collected from study subjects in the Department of Microbiology of our Hospital for direct microscopy of KOH mount and fungal culture on Sabouraud's dextrose agar with chloramphenicol and cycloheximide.

Statistical analysis : Data obtained from the study has been analysed using descriptive statistical methods.

Results

A total number of 1546 paediatric patients visited the Dermatology Outpatient Department of our hospital between July, 2021 to January, 2022 for various skin conditions, of which 306 were diagnosed with dermatophyte infection demonstrating a prevalence rate of 19.79%. Most of the children belonged to 11-15 years age group and there was male preponderance in our study with a male to female ratio of 1.73:1. Children as young as 15 days to as old as 15 years presented with a mean duration of disease of 8.79 ± 12.64 weeks (Figs 1&2). Fourteen children (4.58%) presented with chronic infection (>1 year duration). Most children hailed from rural areas (62.09%) and belonged to poor socio-economic status (64.70%). A positive family history was found in 56.21% patients, 56.87% lived in a joint family set up. 29.41% of patients

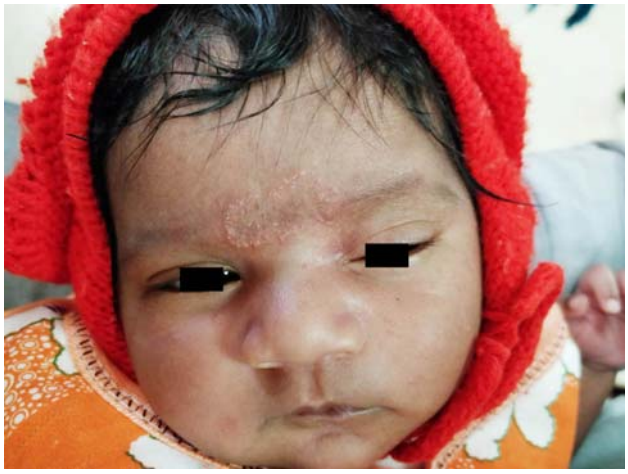


Fig 1 — Single lesion of tinea corporis in a 15-day old infant

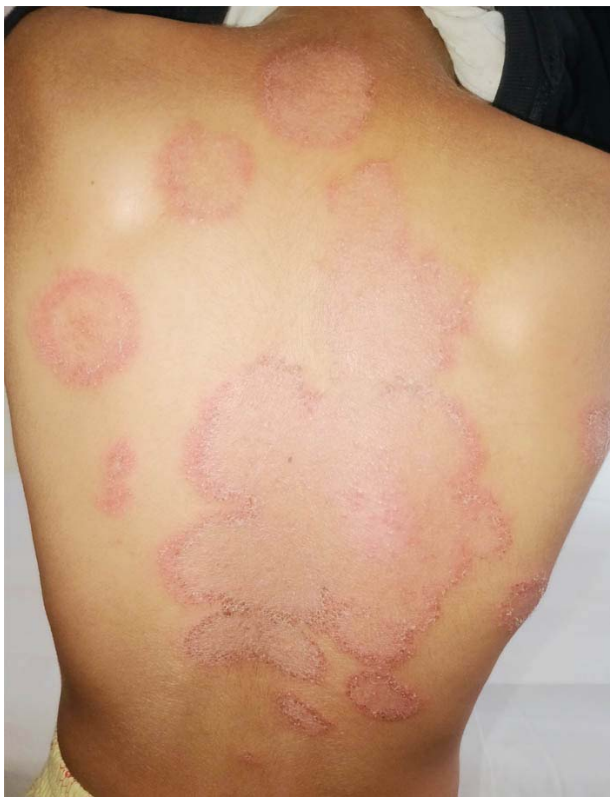


Fig 2 — Extensive tinea corporis in a young boy

Table 1 — *Socio-demographic profile of study participants*		
Variable		No of patients (%)
Sex : M:F = 1.73:1	Male	194 (63.39%)
	Female	112 (36.60%)
Age of presentation (in years) :	Mean ± SD	10.5 years ± 4.06
	Median	12
Age group :	Upto 5 years	42 (13.72%)
	6-10 years	66 (21.57%)
	11-15 years	198 (64.70%)
Duration of illness (in weeks) :	Mean ± SD	8.79 ± 12.6
	Median	44
Regional distribution :	Urban	116 (37.91%)
	Rural	190 (62.09%)
Socio-economic status:	High	24 (7.84%)
	Middle	84 (27.46%)
	Low	198 (64.70%)
Overcrowding (sex separation criterion) :	No overcrowding	106 (45.30%)
	Overcrowding present	128 (54.70%)
Pond bathing :	No	216 (70.59%)
	Yes	90 (29.41%)
Sharing of towel/soap:	No	92 (30.07%)
	Yes	214 (69.93%)
Family member affected/ contact history :	No	134 (43.79%)
	Yes	172 (56.21%)

had habit of bathing in ponds whereas 69.93% of patients shared towels with other family members. (Table 1) We found 14.38% of children to have Co-morbidities of which the most common was Obesity (Fig 3).

Around 8.48% of patients demonstrated a previous history of tinea and 77.12% of patients had already sought medical intervention before presenting to us. Over-the-counter medications was the most common form of treatment received (28.81%) followed by seeking consultation from a general practitioner (25.42%). Dermatologist consultation was sought in only 21.19% of the patients. Among all the patients who had received prior therapy, 61.02% patients had used steroid or steroid-antifungal combination creams (Fig 4)(Table 2).

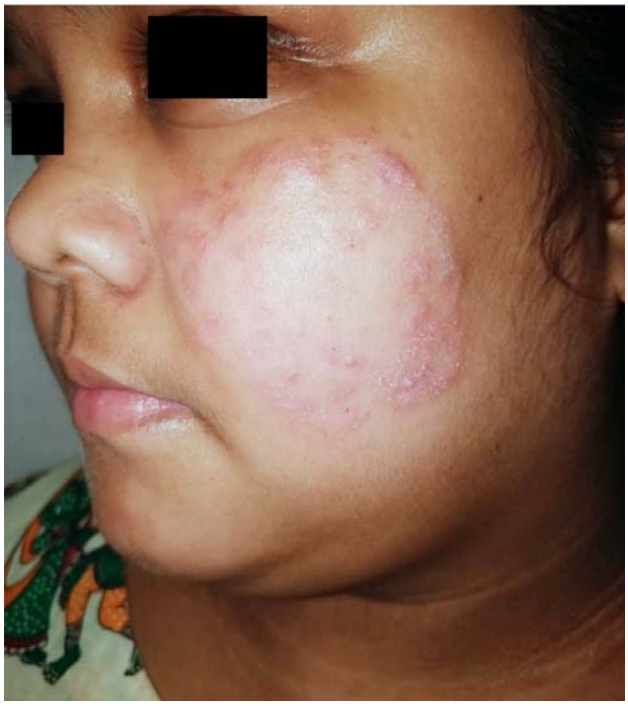


Fig 3 — Tinea faciei in an obese girl

Clinically, the most common presentation was tinea corporis (59.01%) with buttocks being the most common site affected. Around 56.86% children presented with extensive lesions followed by 27.45% presenting with single lesion (Table 3).

Direct microscopy with KOH was positive in 67.32% and growth on fungal culture in 44.44% of cases. In four cases neither KOH mount nor culture could be performed due to insufficient sample (scales were absent). The culture positivity showed the following pattern: *Trichophyton mentagrophytes* in 70 (51.47%), *Trichophyton rubrum* in 54 (39.70%), *Trichophyton tonsurans* in 10 (7.35%), and *Trichophyton verrucosum* in two (1.47%) patients was observed (Table 3).

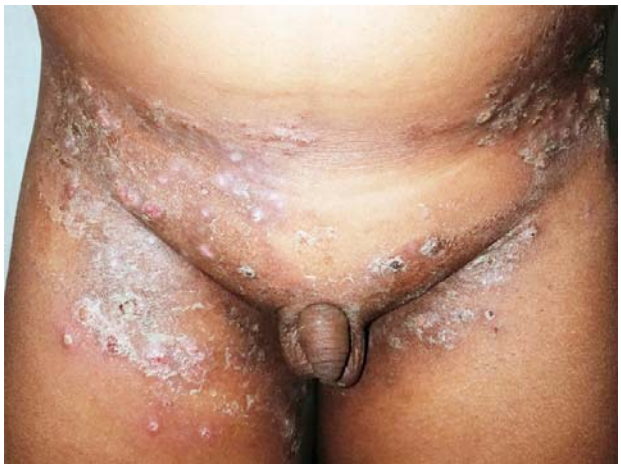


Fig 4 — Steroid modified tinea incognito corporis with cruris

Table 2 — *Treatment profile of study participants*	
Prior treatment received :	
No	70 (22.87%)
Yes	236 (77.12%)
Type of treatment received :	
Topical steroid/ combination creams	144 (61.02%)
Topical antifungals	66 (27.97%)
Topical + oral antifungals	26 (8.50%)
Source of medicine :	
OTC from pharmacy	68 (28.81%)
General Practitioner	60 (25.42%)
Quack	18 (7.63%)
Dermatologist	50 (21.19%)
Recommended by relatives/friends/neighbors	40 (16.95%)

Table 3 — *Clinico-mycological profile of study participants*

Variable	Number of participants (%)
Area of involvement :	
Single lesion	84 (27.45%)
Multiple lesions over a localized area	48 (15.69%)
Extensive	174 (56.86%)
Type of tinea :	
T corporis	128 (41.83%)
T corporis with cruris	104 (33.40%)
T cruris	18 (5.88%)
T faciei	18 (5.88%)
Direct microscopy :	
Positive	206 (67.32%)
Negative	96 (31.37%)
Not done (due to insufficient scales)	4 (1.31%)
Culture :	
Fungal growth positive	136 (44.44%)
Fungal growth negative	166 (54.25%)
Not done	4 (1.31%)
Species isolated :	
Trichophyton mentagrophytes	70 (51.47%)
Trichophyton rubrum	54 (39.70%)
Trichophyton tonsurans	10 (7.35%)
Trichophyton verrucosum	2 (1.47%)

Discussion

The prevalence of tinea among Dermatology Outdoor patients in our study was found to be 19.79%. This was similar to the findings by Gandhi, *et al* (19%)[5]. Other studies have reported a prevalence of 32% (Dash, *et al*) and 44.1% (Dutta, *et al*)[6,7].

Our study had a male predominance with a Male: Female ratio of 1.73 which was similar to previously published studies[3,5-7]. Boys are found to be more engaged in outdoor activities leading to more sweating, greater period of contact with tight clothes leading to higher chances of infection. Females being more conscious of their appearance and practising better personal hygiene could be a possible reason for low rate of infection among them.

Majority of affected children were between 11-15 years which was similar to previous studies[5,7,8] done by Gandhi, *et al*[5], Dutta, *et al*[7], Ray, *et al* while few studies from African countries have found higher frequency of tinea in children <10 years[2,9]. Children of 11-15 years age group spend more time outdoors in activities like tuitions, playing, swimming and thus are in contact with sweaty clothes/ undergarments for longer durations and carry higher chances of contact with the fungus.

The infection was also commonly found in children from rural background (62.09%) and from a lower Socio-economic status which was similar to the findings of Dash, *et al* and Dutta, *et al*[6,7]. This may be due to poor health-care facilities prevalent in these areas and lack of awareness of personal hygiene which plays an important role in the high transmission rates from adults to children within same household. In our study, 29.41% children had the habit of bathing in pond and as high as 69.93% of children shared their soap/ towel with other family members. A positive contact history with an infected family member was reported in 56.21% of children in our study. Other studies on dermatophytosis in children, have documented a contact history with infected family members or close contacts to range from 62.2% to 91.9%[10].

Educating the parents about maintaining personal hygiene, particularly the need to avoid overcrowding, washing clothes separately with hot water each day, avoiding dampness and sharing of clothes and other fomites among children is essential for tackling dermatophyte infection. Other important contributing factors in the occurrence of these infections were a joint family set up, overcrowded housing conditions and contact history with an infected family member.

Dermatophyte infection has been on a steep rise over last few years with a major contributing factor being steroid abuse, incomplete prescriptions and non-adherence to treatment duration. These aspects were highlighted in our study. As many as 77.12% of children had taken some form of treatment before consulting in our outdoor of which only 21.19% had consulted a qualified Dermatologist. Majority of children had applied over the counter medicines (28.81%), followed by visit to a general practitioner (25.42%). Steroid containing topical agents were the most commonly abused drugs seen in as many as 61.02% of children. We are aware of the disturbing trend among several general practitioners who often prescribe steroid-antibiotic-antifungal combination creams in an attempt to cover as many diseases as possible in the absence of an accurate diagnosis. Previous studies have also documented the abuse of TCS creams in children to be in the range of 51% to 94%[10].

In the past, single site involvement was common, with limited area being affected. But, now, infection of multiple sites with widespread infection has become the norm. Our study reported extensive disease in 56.86% of children whereas 27.45% of children presented with a single lesion. This was contrary to past study by Mishra, *et al* who reported a lower percentage of extensive disease (27%)[3]. Few recent studies by Poojary, *et al* and Ray, *et al* have also reported extensive disease in children at the time of presentation (52.2% and 55.2% respectively)[10]. The possibility of occurrence of extensive disease with multiple site involvement has increased with increasing duration of steroid application, use of higher potency of steroids, duration of disease, positive family history,

and more fungal culture positivity rates.

With regard to the clinical features, we found tinea corporis to be the most common type of dermatophyte infection, which was seen in 41.83% of patients, followed by tinea corporis et cruris (33.40%), similar to previous studies[3,5,7,8]. Dash, *et al* have reported an almost equal prevalence of tinea cruris (50%) and tinea corporis (47.47%)[6], whereas Dutta, *et al* have reported tinea faciei to be the most common presentation after tinea corporis[7]. The clinical pattern of superficial dermatophytosis in children is becoming similar to that of adults. This could be attributed to close contact with infected family members, overcrowding and failure to maintain adequate personal hygiene leading to high transmission rates from adults to children within same household.

Direct microscopy was positive in 67.32% cases while other studies have shown a positivity rate as high 85% to 93.8%[7]. Fungal culture was positive in 44.44% cases whereas other studies have shown a positivity range of 60% and 85.1% respectively[7]. The shift in the etiological agent from the more common *T rubrum* to the virulent *T mentagrophytes* complex observed among the adults has been reflected in children too. *Trichophyton mentagrophytes* was the most common species identified followed by *Trichophyton rubrum;* 51.47% and 39.70% respectively. These findings were similar to previous studies by Mishra, *et al*, and Oke, *et al* indicating similar mycological profiles in children and adults[3]. Recent clinico-mycological studies on Paediatric dermatophytosis conducted by Poojary S, *et al* and Ray, *et al* also revealed *Trichophyton mentagrophytes* complex to be the predominant etiological agent (73.7%, 73.18%)[10]. In contrast, Dutta, *et al* have reported *T rubrum* as the most common species[7].

Conclusions

This study marks an increasing trend in dermatophyte infection in the paediatric population and observes the following key points:

- The clinical and mycological profile of superficial dermatophytosis in paediatric population is becoming similar to adults. Breaking the chain of transmission from affected household contacts is a key step to reducing the disease burden in children.
- Lack of awareness regarding personal hygiene among children was an important contributing factor. Parents must be educated about personal hygiene amongst all members which includes avoiding pond bathing, keeping separate towel and soap, not wearing damp clothes, avoiding synthetic garments, for long and keeping the skin folds dry.
- Steroid misuse, treatment non-compliance and incomplete prescription were important factors for high infection rates among children, emerged as leading factors for long duration of infection. Proper awareness of the parents regarding health education, avoidance of self-medication or treatment by unqualified personnel is highly needed to control the disease burden in the society
- Lifestyle modification and weight reduction should be advised for obese children.

Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial Support and Sponsorship : Nil.

Conflicts of Interest : There are no conflicts of interest.

References

1 Pandian J, Balaji RV — A Study on Bacterial Profile of Skin Infections and Antimicrobial Susceptibility of causative organisms among children in a tertiary care hospital. *Int J Curr Microbiol App Sci* 2018; **7(3):** 1827-34.
2 Ogbu CC, Okwelogu IS, Umeh AC — Prevalence of superficial fungal infections among primary school pupils in Awka South Local Government Area of Anambra State. *Journal of Mycology Research* 2015; **2:** 15-22.
3 Mishra N, Rastogi MK, Gahalaut P, Yadav S, Srivastava N, Aggarwal A — Clinicomycological study of dermatophytosis in children: Presenting at a tertiary care center. *Indian J Pediatr Dermatol* 2018; **19:** 326-30.
4 Dogra S, Narang T — Emerging atypical and unusual presentations of dermatophytosis in India. *Clin Dermatol Rev* 2017; **1,Suppl S1:** 12-8
5 Gandhi S, Patil S, Patil S, Badad A — Clinicoepidemiological study of dermatophyte infections in pediatric age group at a tertiary hospital in Karnataka. *Indian J Pediatr Dermatol* 2019; **20:** 52-6.
6 Dash M, Panda M, Patro N, Mohapatra M — Sociodemographic profile and pattern of superficial dermatophytic infections among pediatric population in a tertiary care teaching hospital in Odisha. *Indian J Pediatr Dermatol* 2017; **18:** 191-5.
7 Dutta B, Rasul ES and Bothra A — Tinea epidemic in paediatric population - Clinical pattern with microbiological correlation. *IP Indian J Clin Exp Dermatol* 2022; **8(1):** 1-7.
8 Ray A, Singh BS, Kar BR — Clinico mycological profile of pediatric dermatophytoses:An observational study. *Indian Dermatol Online J* 2022; **13:** 361-5.
9 George IO, Altraide DD— Dermatophyte infections in children: A prospective study from Port Harcourt, Nigeria. *Niger Health J* 2008; **8:** 52-4.
10 Rengasamy M — The Changing Scenario of Dermatophytosis in Children. *Indian Dermatol Online J* 2022; **13(3):** 305-9.

Original Article

Effect of Online Formative Assessment Feedback on Learning Outcomes among Medical Under Graduates

Suchitra Sachin Palve[1], Jui Yeshavant Lagoo[2], Sachin Bhaskar Palve[3]

Background : Formative assessment provides learners with information that allows them to improve their learning and performance. Conducting Online feedback assessments can work as a time-effective alternative, for a large number of students and also help in providing timely feedback.

Objectives : To analyze the impact of Online formative assessment feedback on the academic performance among Undergraduate students.

Methods : This prospective and interventional study was undertaken on MBBS phase I students, age group (≥18 years) of Symbiosis Medical College for women using an Online LMS platform. Students were randomly divided into 2 groups so that the mean marks of both the groups are matched. A formative assessment was conducted with the intent to cover important topics for both the groups subsequently. A set of pre-validated quizzes were administered to the students from both groups; this was followed by an Online feedback session. The students were provided with feedback regarding their performance, based on the checklist prepared. A summative assessment was conducted at the end of the entire system and scores were analyzed in accordance with the marks obtained during online formative assessments.

Results : The Online formative assessment feedback method was well accepted by the students as well as faculty due to its feasibility. There was a significant improvement in the academic performance of the students Post formative assessment feedback sessions. Feedback clearly showed that more than 80% of the students found formative assessment as a comprehensive assessment tool, which helps them in identifying gaps in knowledge, also to test their knowledge more comprehensively and motivates them to work harder.

Conclusion : Online formative assessments have potential advantages for the students as well as for the teacher as they offer flexibility in terms of time and place. Formative assessment feedback will help the student to understand the expectations of the teacher along with identification of learning gaps. [*J Indian Med Assoc* 2023; **121(10):** 37-41]

Key words **: Assessment, Feedback, Formative, Online.**

Formative assessment is crucial in guiding the learning process and has a powerful effect on learning outcomes as well as attitude towards learning[1-5]. The newly implemented Competency Based Medical Education (CBME) is organized around competencies focusing on curricular outcomes, thus mandating assessment processes that are continuous, frequent, criterion-based and developmental[3]. Formative assessment is the assessment for learning and provides information that allows learners to improve learning and performance. In order to achieve this, FA needs to be included as a built-in component of curriculum[15].

Conventional paper based assessments have several limitations attributed to the long process and logistics involved. They are associated with constraints to provide individualized feedback to the large number of students[11-12]. Online formative assessments have potential advantage of offering flexibility in terms of time and place and ability to provide immediate feedback to the student by the teacher. Learning can be further augmented by sharing study links and resources[14,21].

Evidence to support the educational benefits of online formative assessment feedback is relatively limited. Literature has contradictory reports showing that formative assessments do not improve the learning outcomes of students[1,6,14], whereas others demonstrating a positive effect on students' performance in summative examinations[2,3,8,12,20].

Editor's Comment :

- Online Formative assessment feedback in medical education is crucial because it provides ongoing, constructive input to students as they progress in their learning. It helps students understand their strengths and weaknesses, enabling them to identify areas for improvement and adjust their study strategies accordingly. This timely feedback not only supports individual student growth but also contributes to the overall enhancement of the quality of medical education and ultimately leads to better-prepared healthcare professionals.

Dr S S Tantia MCH & RC, Sri Ganganagar, Rajasthan 335002

[1]MD, Professor and Head, Department of Physiology and Corresponding Author

[2]MD, Professor, Department of Emergency Medicine, Bharati Vidyapeeth (deemed to be university) Medical College, Pune, Maharashtra 411043

[3]MD, Professor and Head, Department of Community Medicine

Received on : 15/09/2022

Accepted on : 20/10/2023

The unprecedented COVID-19 pandemic led to a crisis situation, has forced the medical colleges to cope by adopting digital mode and restructuring T-L and assessment methods. This methodology worked as a time effective alternative and also allowed conduct of FA for a large number of students. Continuation of hybrid mode of teaching and assessment is the need of the hour attributed to resurgence of COVID waves.

The present study was undertaken to understand the impact of Online formative assessment feedback for improving the academic performance during summative among Undergraduate medical students.

Materials and Methods

Study setting : The study was undertaken in Symbiosis Medical College for Women using an Online Learning Management System (LMS) platform. Medical Undergraduates from phase I admitted during the academic year 2020-2021 were recruited for the present study.

Sampling technique : Convenient sampling technique where the entire class was the part of the ongoing process of formative assessment after each module.

Study Duration - 6 months

Type of study - Prospective interventional

Methodology :

The study was initiated after taking prior ethical clearance (SIU/IEC/264).

Faculty members from the Department of Physiology were trained by the departmental LMS co-ordinator in conducting Online formative assessment. They were also sensitized and trained for providing Online feedback which covered following points.

(a) What was done well ?

(b) What went wrong ?

(c) Plan for further improvement.

Online formative assessments as quizzes were created, peer reviewed and validated by subject experts within the department who had more than five years of teaching experience. Each quiz consisted of 10 multiple choice questions (multiple choice, true or false and extended matching type) covering all levels of cognition namely, recall, comprehension, reasoning and application.

To calculate the reliability of the research tool which in our case was the feedback questionnaire, the method of test and retesting (Test - Retest) was adopted with a difference of a two-week time. Feedback questions were given to a group of 25 female students and the reliability coefficient was calculated which was 0.84.

Informed consent was obtained from all the participants. After first internal assessment examination, based on the marks obtained; students were randomly divided into 2 groups ie, Group A and Group B, in such a way that the mean marks of both the groups were matched. Group A (n=71) and Group B (n=79). At the end of each important topic of Cardiovascular System and Respiratory System, formative assessments were conducted. A set of pre-validated quizzes were administered to the students from both groups, through a learning management system (MOODLE). Feedback was provided to a particular group of students by the allocated faculty after each formative assessment.

Summative assessment was conducted at the end of the entire system and scores were analyzed in comparison with the marks obtained during Online formative assessments.

After completion of summative assessment, students were provided with the following questionnaire and their responses were noted.

Questionnaire for assessing perceptions of students. (Closed ended questions for analysis on Likert scale)

(1) Does the given assessment test your knowledge for the module more comprehensively?

(2) Did the assessment help you in identifying gaps in knowledge?

(3) Will this assessment help you to analyze how much you need to read more for the given module?

(4) Do you feel that the formative assessment will help you to gain more knowledge for the given module?

(5) Does it motivate you to work hard?

Students were also given open ended questions asking them how and which ways did they find the feedback sessions helped in improving their academic performance.

Statistical Analysis : All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean ± Standard Deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. The difference of the means of analysis variables between two time points in same group was tested by paired 't' tests. Data were analyzed using SPSS software v.23(IBM Statistics, Chicago, USA) and Microsoft Office 2007. p-value <0.05, was considered to be statistically significant.

Results

There was a statistically significant improvement in the academic performance of the students Post formative assessment feedback sessions during the internal assessment, especially the student who secured blow average marks were benefitted by these

sessions (Tables 1&2). Feedback clearly showed that more than 70% of the students found formative assessment as a comprehensive assessment tool, which helps them in identifying gaps in knowledge, also to test their knowledge more comprehensively and motivate them to work harder (Table 3). Post internal assessment feedback session which was based on open ended responses showed that most of the students felt that feedback sessions were beneficial, useful, important, informative and helped them to identify the learning gaps (Table 4).

Table 1 — *Distribution of students according to IA Marks*

IA Marks	No of students	Percent
<33	0	0
33-60	13	8.7
60-75	125	83.3
75-100	12	8
Total	150	100

Table 2 — *Change in average marks*

FA Marks	FA Marks (out of 100)		IA Marks		Mean change	p value
	Mean	SD	Mean	SD		
<33	26.9	5.5	66.6	9.4	39.8	0.010*
33-60	49.4	5.6	66.1	6.0	16.7	<0.001*
60-75	63.8	4.3	67.2	8.0	3.3	0.013*
75-100	79.6	4.5	68.8	6.0	-10.8	<0.001*
Overall	60.0	13.9	67.0	6.8	7.1	<0.001*

Note : p value* significant at 5% level of significance (p<0.05)

Discussion

The present study tries to outline the method for providing Online formative feedback to a large cohort of students during phase I MBBS for Physiology subject. It is a time-effective alternative allowing to conduct formative assessment for a large number of students and also helps to provide timely feedback to the learner. Online formative assessment has received much less attention as compared with the conventional method of face-to-face mode and inadequate qualitative information is available on FA in higher education contexts[18]. Feedback can become a part of the learning cycle that will help the learner, the teacher, and even the teaching program[19,20].

The use of digital tools has made the process of giving and receiving feedback more accessible for learners[30]. It has been reported that computer-mediated feedback in Online courses contributes to student learning[4]. Indeed, studies have shown that providing feedback increases retention of knowledge and results in improvement in final grades.

Several benefits of Online feedback provided to students upon completion of Online formative assessment have been reported. Use of technology helps in individualizing feedback which in turn facilitates learning by identifying the learning gaps[1]. In addition, technology can be employed to analyze students' performance, keep track of their progress and modify method of teaching to meet the specific needs of students[26,27]. Studies have shown that feedback received through online self-assessment[23] can enable learners to self-monitor their learning. It facilitates healthy communication between teacher and the student[20].

In order to maximize the benefit of FA, literature has provided suggestions for timing of submission of FA as well as feedback session. Studies have also shown that complex task performance will get benefited with a delayed feedback as it will ensure sufficient reflection time. In our study, we allowed the students to submit their responses within a time frame of 30 minutes to ensure that they will not read the study material during the quiz as it will be difficult for them to respond if they have not prepared. Few reports have suggested that, for improved academic performance timed assessments are useful, rather than untimed ones[15,16]. It has been suggested that feedback should be inclusive of whether the performance was as per expectation, and should incorporate further information to enhance knowledge and corrective measures allowing improvement[8,18,24]. The methods adopted in the present study not only ensured the convenient timely feedback but also ensured availability

Table 3 — *Effect of Online Formative Assessment Feedback on Learning Outcomes among Medical Under graduates*

Parameters	Disagree		Agree		Neutral		Strongly agree		Strongly disagree	
	N	%	N	%	N	%	N	%	N	%
Does the given assessment test your knowledge for the module more comprehensively?	0	0.0	107	72.3	10	6.8	31	20.9	0	0.0
Are you able to identify the gap in knowledge after the assessment?	1	0.7	93	62.8	9	6.1	45	30.4	0	0.0
Will this assessment help you to analyze how much you need to read more for the given module?	0	0.0	87	58.8	7	4.7	53	35.8	1	0.7
Do you feel that the formative assessment will help you to gain more knowledge for the given topics?	3	2.0	85	57.4	20	13.5	38	25.7	2	1.4
Does it motivate you to work hard?	2	1.4	88	59.5	8	5.4	50	33.8	0	0.0
Did formative assessment Feedback helped you for scoring more in the internal assessment ?	0	0.0	63	42.6	14	9.5	70	47.3	1	0.7

Table 4 — *Themes derived from the responses obtained from students*

- **Feedback sessions were beneficial for comprehensive learning.**
- Questions asked during the test were of wide range and covered all difficulty levels.
- The questions were interesting right from the basic concepts to the applied part of the topic.
- There were wide variety and range of questions in the test which covered the ABC of the topic.
- **Identification of learning gaps.**
- I could understand where I was lacking while writing the answers.
- It helped me to understand where I am lacking.
- Feedback session was very useful, never know what I got wrong in other exams so it's nice to know where I went wrong."
- **Provided focus for learning.**
- Despite performing well, it showed me where I could improve, or where common mistakes were made to keep in mind for next time.
- This process made easy for me to understand my mistakes and also how to correct them.
- I could identify my mistakes and was guided by teacher regarding how to rectify them.
- The interaction with teacher helped me to understand where I actually went wrong.
- **Helpful expected level of knowledge.**
- Any type of feedback is always good. I also find this a benefit as this is my first exam during MBBS.
- You must know in terms of study, how in-depth one has to go to be prepared for the exam.
- Very helpful - good to know common errors and where I went wrong in exams.
- **Two was communication interactive nature was helpful.**
- This style of feedback should be implemented in all [courses].
- The feedback session is a good concept, especially when you have a class that is over 150 students you get a lot of benefit.
- This two-way communication between me and my teacher was very helpful.
- This process of exam is super cool as it also takes an accountability of my inputs.
- Teacher asked about my comments and inputs regarding the exam which is really good.
- It was non-threatening as teacher was explaining us how to improve.
- The feedback session was very nice as teachers were explaining us where we went wrong in a non-threatening manner.
- **Helped to prepare plan of action.**
- This process made easy for me to understand my mistakes and also how to correct them.
- I could identify my mistakes and was guided by teacher regarding how to rectify them.
- The feedback sessions helped me to understand the road ahead for planning my studies.
- Feedback helped me to plan the way I study
- I could plan my studies well after receiving the feedback.

of an adequate time to reflect on what and how things went wrong and how they can be corrected by feedback mechanism[17].

In this study, students were informed regarding the topics which needs to be emphasized and also the topics which will need in-depth preparation. Studies have suggested that formative assessment can deeply affect students; so feedback should be provided in a manner that encourages positive motivational beliefs and self-esteem[19]. A good verbal and non-verbal communication skill will have a positive motivational impact on students. A proper voice tone, body language of a teacher and active listening will help in escalating the dialogue between the teacher and the learner. In the present study, the students described the feedback session as useful, informative, interactive and non-threatening which is in alignment with earlier studies recommending the feedback to be an interactive dialogue, not a monologue[12,13]. It should be personalized, not generalized. It has been suggested that discussion between learner and facilitator in a language easily understood will encourage students to elaborate their issues and concerns[25]. The feedback method of the present study did aim to provide more personalized feedback to a large cohort of students through Online platform which thoroughly ensures maintaining confidentiality, and privacy. The recommendation provided by Craig and Glover that feedback should be interactive, a dialogue, not a monologue, personalized, not generalized and presented in easy-to-understand language[5]. He also added that the feedback should not be the final process of learning during a task; instead, it must be a springboard toward improving future assessments, aptly referred to as feedforward[2]. This was corroborated by Kerridge who suggested that encouraging discussion between learner and facilitator will allow the students to elaborate their issues and concerns in a language that is accessible and readily understood, which may be achieved using the method described in the present study[14]. A study conducted by Price, *et al* identified difficulties of accurately measuring the aspects of feedback that truly influence the learner and the learning process in a meaningful and lasting manner[16].

We would also like to elaborate the additional benefits of using the digital platform for FA. Use of technology allows easy access to assignments using individual password reducing administrative load of manual correction and evaluation of assessment of answer sheets.

It can facilitate student engagement, bilateral discussion and helps to discover and respond to

underlying misconceptions.

Limitations :

- This method was only adopted for one term, so there is a need to explore its feasibility and sustainability of the process.
- There is a question of feasibility with respect to training of faculty for using technology, availability of robust LMS system and institutional support.
- As this process was conducted for only one system, reliability needs to be proved.

Future directives :

We propose that this tool should be applied for all systems in Physiology and can be introduced at institutional level.

Conclusion

The present study proposed a method of providing timely formative feedback to a large cohort of first-year Physiology class in a manner that achieved.

The Online formative assessment feedback method was well accepted by the students as well as faculty who perceived the technique to be feasible and flexible in terms of time and place.

It was perceived by the students that formative feedback was helpful in comprehensive learning with identification of gaps and improved learning outcomes. There was an improvement in students' performance in summative assessment, implying a positive academic impact.

References

1 Ai H — Providing graduated corrective feedback in an intelligent computer-assisted language learning environment. *ReCALL* 2017; **29(3):** 313-34.
2 Bennett N, Kell J — A Good Start? Four Year Olds in Infant Schools. New York: Simon & Schuster Education, 1989.
3 Beebe R, Vonderwell S, Boboc M — Emerging patterns in transferring assessment practices from F2F to online environments. *Electronic Journal of e-Learning* 2010; **8(1):** 1-12.
4 Bahari A — Computer-mediated feedback for L2 learners: Challenges versus affordances. *Journal of Computer Assisted Learning* 2012; **37(1):** 24-38.
5 Craig C, Glover C — Feedback and feed-forward. In: *Assessment: Re- sources, References and Tools for Assessment in the Biosciences*. Leeds: UK Centre for Bioscience, Leeds Metropolitan University, 2009.
6 Dunn L, Morgan C, O'Reilly M, Parry S — The Student Assessment Handbook: New Directions in Traditional and Online Assessment. Lon- don: Routledge, 2003.
7 Fisher R, Cavanagh J, Bowles A — Assisting transition to university: using assessment and feedback as a formative learning tool. *Assess Eval High Educ* 2011; **36:** 225-37.
8 Fitzpatrick S — The challenge of teaching law subjects with large and diverse student cohorts. *J Austr Law Teach Assoc* 2009; **2:** 113-9.
9 Handley K, Price M, Millar J — Engaging Students with Assessment Feedback. Oxford: ASKe, Oxford Brookes University, 2008.
10 Hattie J — Influences on Student Learning. Auckland: Inaugural Lecture, Professor of Education, University of Auckland, 1999.
11 Hattie J, Timperley H — The power of feedback. *Rev Educ Res* 2007; **77:** 81-112.
12 Hounsell D, McCune V, Hounsell J, Litjens J — Investigating and Enhancing Guidance and Feedback to Undergraduate Students. Northum- bria: Third Biennial Northumbria/EARL SIG Assessment Conference, 2006.
13 Jordan J — The Use of Orally Recorded Exam Feedback as a Supplement to Written Comments (online). http://www.amstat.org/publications/jse/ v12n1/jordan.html [20 July 2016].
14 Kerridge A — Feedback for Success. Wellington, New Zealand: 16th International First Year in Higher Education Conference, 2013.
15 Kift S, Moody K — Harnessing Assessment and Feedback in the First Year to Support Learning Success, Engagement and Retention. Melbourne: ATN Assessment Conference, RMIT University, 2009.
16 Kluger A, DeNisi A — Feedback interventions: toward the understanding of a double-edged sword. *Curr Dir Psychol Sci* 1998; **7:** 67-72.
17 Lawrie G, Wright A, Schultz M, Dargaville T, O'Brien G, Bedford S, *et al* — Using formative feedback to identify and support first-year chemistry students with missing or misconceptions. A practice report. *Int J FYHE* 2013; **4:** 111-6.
18 McLaughlin T, Yan Z — Diverse delivery methods and strong psychological benefits: A review of online formative assessment. *Journal of Computer Assisted Learning* 2017; **33(6):** 562-74.
19 Nicol D — Principles of Good Assessment and Feedback: Theory and Practice. Glasglow: REAP International Online Conference on Assess- ment Design for Learner Responsibility, University of Strathclyde, 2007.
20 Price M, Handley K, Millar J, O'Donovan B— Feedback: all that effort, but what is the effect? *Assess Eval High Educ* 2010; **35:** 277-89.
21 Price M, O'Donovan B — Making Meaning Out of Assessment Feedback– Getting More than the Message. Adelaide, SA, Australia: HERDSA Annual Conference–Enhancing Higher Education, Theory and Scholar- ship, 2007.
22 Price M, Rust C — Feedback on Exams. Oxford: Discussion Paper for Brookes Student Learning Experience Conference, Oxford University, 2009.
23 Priestley J — Designing First-Year Assessment and Feedback: a Guide for University Staff. Leeds, UK: First Level Assessment and Feedback Proj- ect, Leeds Metropolitan University, 2009.
24 Pe´rez-Segura JJ, Sa´nchez Ruiz R, Gonza´lez-Calero JA, & Co´zar-Gutie´rrez R — The effect of personalized feedback on listening and reading skills in the learning of EFL. Computer Assisted Language Learning 2020. https://doi.org/10.1080/09588 221.2019.1705354
25 Race P — Putting Feedback Right: Getting Better Feedback to More Students in Less Time. Leeds, UK: Designs on Assessment Conference, Leeds Metropolitan University, 2009.
26 Radloff A, Coates H – Doing More for Learning: Enhancing Engagement and Outcomes. Camberwell: Australasian Survey of Student Engagement Report, Australian Council for Educational Research, 2010.
27 Ramsden P — Learning to Teach in Higher Education (2nd ed). London: Routledge, 2003.
28 Sadler R — Formative Assessment and the Design of Instructional Systems. *Inst Sci* 1989; **18:** 119-44.
29 Shute VJ — Focus on formative feedback. *Rev Educ Res* 2008; 78: 153-89.
30 Yilmaz R — Exploring the role of e-learning readiness on student satisfaction and motivation in flipped classroom. *Computers in Human Behavior* 2017; **70:** 251-60.

Original Article

Assessment of Seminar-based Teaching in Medical Education : Students' Point of View

Kusum Singla[1], Sameena Khan[2], Munish Kumar[3]

Background : The lecture is the centered, traditional method of teaching a large group in which students participate passively which makes the studies teacher-centered, boring, tired and exhausting. Nowadays according to some studies, students are more interested in active learning as it makes the topics more interesting. Moreover, the new curriculum in medical sciences also emphasizes more on small group discussions and active learning. So present study aimed to evaluate the student's point of view on seminars as a learning teaching method.

Materials and Methods : The present study was undertaken with the first professional MBBS students of our college in the department of Biochemistry in which 102 learners participated. Students were divided into groups of 8 and topics were allotted to each group. After the seminar feedback was collected from all the students in form of a self-designed questionnaire.

Results : Overall, 61 students agreed that seminars evoke more interest in the topic as compared to lectures. Out of 102, 38 were neutral regarding whether the seminars are time-consuming or not. 55 students agreed that seminars help them better understand the topic than the lectures whereas 14 were strongly agreed with the same. In the present study 59 (58.4%) of the students think that classroom learning was more satisfactory in terms of knowledge gain than the seminars.

Conclusion : Our present study learners agreed that seminars are time-consuming but evoke more interest and a better understanding of the topic. Also demonstrated that seminars encourage the motivation for self-study and also enhance confidence. But views are almost neutral regarding whether classroom teaching is better or seminars. Further studies including a larger number of participants will be useful for a better understanding of the topic.

[*J Indian Med Assoc* 2023; **121(10):** 42-3]

***Key words* : Seminars, Lectures, Students, Teaching.**

In India teaching is still dominated by lectures[1]. The lectureis the traditional method of teaching a large group in which students participate passively. Studies have reported that teacher-centered teaching makes the students bored, tired and exhausted causing a decrease in concentration that results in sleeping in class or may be absence from the class[2]. Because the new curriculum is competency-based and emphasizes small group discussions, seminar presentations by the students are promoted[3]. The Seminar is a small group teaching method in which students are divided into small groups, a topic is allotted and the under the guidance of the teacher, students discuss among themselves and prepare the presentation[4]. Seminars not only allow the active participation of the students but also give them confidence and the chance to independent and flexible thinking and learning. Presentations help the students to conquer their nervousness and inspire them to discuss their views without any hesitation[5]. Moreover, seminars also motivate them for lifelong self-directed learning that helps in developing competent medical Graduates. So, present study aimed to evaluate the students' point of view on seminars as a learning teaching method.

Editor's Comment :

- Lectures make the students bored, tired and exhausted causing decrease in concentration, sleeping and absence from the class. Seminars allow active participation and help them to concur their nervousness and present their views without any hesitation. So present study was carried out to evaluate the student's point of view on seminars as their teaching and learning method.

Materials and Methods

The present study was undertaken with the first professional MBBS students of our college in the department of Biochemistry. All 102 learners consented to be a part of the study and all participated.

Students were divided into groups of 8 and topics were allotted to each group. All students of each group were asked to prepare their respective topics as anyone in the group can be called for a presentation. Other

[1]MBBS, MD, Associate Prpfessor, Department of Biochemistry, Army College of Medical Sciences, Delhi 110010

[2]MBBS, MD, Associate Professor, Department of Microbiology, Dr D Y Patil Medical College, Hospital and Research Center, Maharashtra 411018

[3]MBBS, MD, DNB, Associate Professor, Department of Anaesthesiology and Critical Care, Command Hospital (Central Command), Uttar Pradesh 226002 and Corresponding Author

Received on : 19/01/2023

Accepted on : 02/04/2023

groups also have to prepare all the topics as they will be given a chance to clarify their doubts and marks for each valid question. The resenting group also prepared questions for the other groups and marks will be awarded for each question asked by the presenting group and for each answer that is answered by the other group. This method makes all the students study all the topics thoroughly.

Table 1 — *Feedback of the students to the different points of the seminar*

Feedback	Frequency (Percentage) [N=102]				
	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Bring up the interest in the topic	17(16.7%)	61(59.8%)	22(21.6%)	Nil	2(2%)
Seminars are time consuming	10(9.8%)	21(20.6%)	38(37.3%)	29(28.4%)	4(3.9%)
Better understanding of the topic	14(13.7%)	55(53.9%)	25(24.5%)	7(6.9%)	1(1%)
Stronger recollection of the topic	16(15.7%)	55(53.9%)	28(27.5%)	3(2.9%)	Nil
Motivate self directed learning	25(24.5%)	60(58.8%)	16(15.7%)	1(1%)	Nil
Enhance confidence	32(31.4%)	55(53.9%)	14(13.7%)	1(1%)	Nil
Better than classroom teaching learning	8(7.8%)	29(28.4%)	46(45.1%)	13(12.7%)	6(5.9%)

Results

After the conduction of the seminars, feedback was collected from the students in the form of questionnaires and the results are summarized in Table 1.

Discussion

Traditional lecture-based teaching is one of the widely used methods of teaching not only in the medical field but in all streams. Several methods have been developed over time both for teaching as well as assessment. Although, the seminar is also not a very new method and can be used for both teaching purposes as well as for assessment. This not only improves confidence but is also important for improving communication skills. This study is based on students' responses regarding the seminar-based teaching method.

76.5% of the learners agreed that seminars bring interest in the topic, of which 16.7% strongly agreed. No one disagreed with this. A study by Thomas PC, *et al* reported almost similar results (86.1% of students agreed and of them, 41.9 % strongly agreed)[2]. 37.3% of students were neutral regarding the more time-consuming seminars.A study by Patel, *et al*[1] reported 69.1% agreed with the time consumption, whereas 12.7% were neutral. 67.6 % agreed that seminars are more helpful in better understanding the topic and of them, 13.7% strongly agreed. Thomas PC, *et al* study reported 90.7% agreed to the same. Only 7.8 % strongly agreed that seminars are better than classroom learning.

We all somehow believe that learning is best achieved by the active participation of the students with more open discussion in a relaxed environment. This also supports by earlier researchers. However, lectures are the most widely used methods of teaching that provide an overview of the topic of the subject[6]. Like seminars, lectures cannot be used for assessment purposes but can serve useful instructional functions[7]. lectures encourage passive learning with more of the teachers' talk and the least participation of the students[8,9]. In the present study 59 (58.4%) of the students think that classroom learning was more satisfactory in terms of knowledge gain than the seminars.

Conclusion

Our present study learners agreed that seminars are time-consuming but evoke more interest and a better understanding of the topic. Also demonstrated that seminars encourage the motivation for self-study and also enhance confidence.But views are almost neutral regarding whether classroom teaching is better or seminars. Further studies including a larger number of participants will be useful for a better understanding of the topic.

References

1 Jitendra RP, Dharmik SP, Rajesh D, Jasmin P, Ravi T, Nikita D — et al.Evaluation of student seminar in medical education: students' perspective. *Int J Cur Res Rev* 2015; **7(7):** 6-9.

2 Schreiber EB, Fukuta J, Gordon F — Live lecture versus video podcast in undergraduate medical education: A randomised controlled trial. *BMC Medical Education* 2010; **10:** 68.

3 Bonwell C, Eison J — Active Learning: Creating Ex-citement in the Classroom AEHE-ERIC Higher Education Report No. 1. 1991. Washington DC: Jossey-Bass.

4 Thomas PC, Radha TR, Subitha K — Comparison of effectiveness of lecture and seminar asteaching-learning methods in Physiology with respect to cognitive gain and student satisfaction. *J Evolution Med Dent Sci* 2017; **6(59):** 4357-62.

5 Jain A, Bansal R, Singh KD, Kumar A — At-titude of medical and dental first year students towards teaching methods in a medical college of northern In-dia. *Journal of Clinical and Diagnostic Research* 2014; **8(12):** XC05-XC08.

6 Earl S, McConnell M, Middleton I — Postgraduatecertificate in tertiarylevel teaching. Aberdeen: TheRobert Gordon University, Educational & StaffDevelopment Section, Centre for the Enhancement ofLearning & Teaching. 1998. www2.rgu.ac.uk/celt/pgcerttlt/.

7 Kaur G — Study and analysis of lecture model ofteaching. I*nternational Journal of Educational Planning & Administration* 2011; **1(1):** 9-13.

8 Doucet MD, Purdy RA, Kaufman DM, Langille DB — Comparison of problem based learning and lecture format incontinuing medical education on headache and management. *Med Educ* 1998; **32:** 590-96.

9 Hrepic Z, Zollman DA, Rebello SN — Comparing students and experts' understanding of the content of a lecture. *J Sci Edu Tech* 2007; **16:** 213-24.

Original Article

Efficacy and Safety of Afatinib as Second-line Treatment in Advanced Squamous Cell Carcinoma of the Lung : A Retrospective Observational Study

Sk Haidar Ali[1], Suvra Mondal[2], Santu Mondal[3], Amitabha Chakrabarti[4]

Background : Lung Squamous Cell Carcinoma (SqCC) is a challenging subtype of Non-small Cell Lung Cancer with limited treatment options and poor prognosis. Afatinib, an irreversible ErbB family blocker, has shown efficacy as a second-line option after platinum-based Chemotherapy but its role in Indian patients is unclear.

Aims and Objectives : To evaluate the effectiveness, safety and Quality of Life (QoL) of afatinib in Indian patients with advanced lung SqCC after platinum-based chemotherapy.

Materials and Methods : This retrospective study included 110 patients with stage III or IV lung SqCC who received first-line chemotherapy followed by afatinib. Tumor assessments were performed every 8 weeks until progression, Adverse Events (AEs) were graded using CTCAE and QoL was assessed using GHS/QoL scale.

Results : The median age was 65 years, 83.6% were males, 84% were non-smokers and 80% were at stage IV. Afatinib resulted in a median Progression Free Survival (PFS) of 3.7months, an Overall Response Rate (ORR) of 9.7%, and a Disease Control Rate (DCR) of 45%. The most common grade 2 AEs were Diarrhea (38%), Rash/acne (32%) and Stomatitis (11%) and the most common grade 3 AEs were Diarrhea (7%) and Stomatitis (3%). QoL improved in 31.7% of patients, pain reduced in 36.7%, cough alleviated in 41.7% and dyspnea improved in 55%. These findings are consistent with the LUX-Lung 8 trial.

Conclusions : Afatinib is an effective and safe second-line treatment for advanced lung SqCC after platinum-based chemotherapy in Indian patients. Afatinib also improves QoL and symptom control in this population. Future research should explore biomarkers and resistance mechanisms to afatinib in lung SqCC.

[*J Indian Med Assoc* 2023; **121(10):** 44-7]

Key words **: Afatinib, Lung Squamous Cell Carcinoma (SqCC), Second-line Treatment.**

Lung cancer is the most common and deadly type of Cancer Worldwide[1]. Lung Squamous Cell Carcinoma (SqCC) is a subtype of Non-small Cell Lung Cancer (NSCLC) that affects 20-30% of NSCLC patients[2]. Unlike lung adenocarcinoma, another subtype of NSCLC, lung SqCC has limited treatment options and poor prognosis[3]. Lung SqCC is characterized by high genetic diversity and complexity, with mutations in many genes and pathways[2,4]. Some of these mutations affect the Epidermal Growth Factor Receptor (EGFR), which is a target for some drugs[4,5]. However, the EGFR mutations in lung SqCC are different from those in lung adenocarcinoma and the response to EGFR inhibitors is usually low and short-lived[5,6].

The standard first-line treatment for advanced/metastatic lung SqCC is Chemotherapy or Immunotherapy, either alone or in combination[7,8]. Immunotherapy is a type of treatment that boosts the Immune system to fight cancer cells[8]. Pembrolizumab is an example of an immunotherapy drug that works by blocking a protein called PD-1 on immune cells[9]. However, not all patients benefit from Immunotherapy, and some may develop resistance over time[10]. For patients who progress after first-line treatment, there are few effective options available. The choice of second-line or later treatment depends on the previous treatment and the patient's condition. Generally, drugs with different mechanisms of action are preferred to avoid cross-resistance[11,12].

Afatinib is a drug that blocks the signaling of all ErbB family members, including EGFR[13]. Afatinib has shown efficacy in patients with EGFR mutation-positive NSCLC and is approved as first-line treatment in this indication[14]. However, afatinib is not recommended as

Editor's Comment :

- Afatinib offers an effective treatment alternative for advanced Squamous Cell Carcinoma lung in place of costly Immunotherapy in our real world scenario. It also has the benefit of oral domiciliary treatment with manageable toxicity profile.

Department of Radiotherapy, R G Kar Medical College & Hospital, Kolkata 700004

[1]MBBS, MD (Radiotherapy), Medical Teacher Trainee Reserve

[2]MBBS, MD (Radiotherapy), Senior Resident

[3]MBBS, MD (Radiotherapy), Assistant Professor, Department of Radiotherapy, IPGME&R Medical College & Hospital, Kolkata 700020

[4]MBBS, MD (Radiotherapy), Associate Professor and Corresponding Author

Received on : 01/09/2023

Accepted on : 04/10/2023

first-line therapy for unselected patients with Squamous Cell Lung Cancer and wild-type EGFR[7,15]. Afatinib has demonstrated efficacy as second-line therapy in patients with metastatic Squamous Cell Lung Cancer following progression on Platinum-based chemotherapy, and is approved by the US FDA for use as monotherapy in this patient population[13]. However, the inclusion of afatinib as a second-line treatment option for patients with Squamous Cell Lung Cancer varies across treatment guidelines, reflective of the changing treatment landscape in recent years. The approval of afatinib for use in patients who have progressed on Platinum-based Chemotherapy was based on results from the open-label, Phase III LUX-Lung 8 study, which compared the second-line use of afatinib with erlotinib in patients with advanced Squamous Cell Lung Cancer[15]. Currently, there is a paucity of data on outcomes of afatinib treatment in Indian patients with advanced SCC of the lung.

Aims and Objectives

- To assess the efficacy of afatinib treatment in Indian patients with advanced SqCC of the lung who were treated prior platinum-based Chemotherapy.
- To evaluate the patient-reported outcomes of afatinib treatment in these patients, including Quality of Life (QoL).

Materials and Methods

This is a Retrospective study of 110 patients conducted from January, 2019 to December, 2022 with advanced/metastatic SqCC of the lung who received first-line Platinum-based-Chemotherapy, followed by Afatinib. Afatinib (40 mg) was given orally once daily and adjusted according to tolerability. Treatment was continued until disease progression, unacceptable AEs or withdrawal. Eligible patients were aged 18 years or older with stage IIIor IV NSCLC of squamous histology who progressed after at least four cycles of platinum-based Chemotherapy. Other inclusion criteria were: ECOG performance status within 2, measurable disease, and adequate organ function.

Exclusion criteria : Previous treatment with EGFR-targeted agents; active brain metastases; radiotherapy within 4 weeks; other malignancies within the past 3 years; pre-existing interstitial lung disease; significant gastrointestinal or cardiovascular disorders; any serious illness or organ dysfunction; active hepatitis B, C, or HIV infection; contraindications for afatinib; hypersensitivity to afatinib or its excipients; major surgery within 4 weeks; previous participation in an afatinib trial; use of any investigational drug within 4 weeks; and patients without progressive disease.

Tumour assessments were done by CT or MRI scan at baseline and every 8 weeks until progression or withdrawal. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0). Safety laboratory assessments were done at baseline, on the first visit of each cycle, and at the end of treatment. Patient-reported outcomes were assessed at the first visit of each cycle using Global Health Status/Quality of Life (GHS/QoL) scale.

The aims were to assess Progression Free Survival (PFS), Objective Response Rate (ORR) and Disease Control Rate (DCR), defined as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) and incidence of moderate to severe Adverse Events (AEs).

Results

Demographic characteristics and pertinent medical history data were extracted from the medical records of the 110 patients diagnosed with advanced/metastatic Squamous Cell Carcinoma (SqCC) of the lung who were included in the study.

Among the total cohort of 110 patients, a majority of 83.6% (N=92) were identified as male and their median age was 65 years (range: 36-84 years).

The baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) distribution revealed that 65.5% (N=72) of the patients were categorized under ECOG PS 1, followed by 31.8% (N=35) of patients who were classified as ECOG PS 0 (Table 1).

Within the cohort of patients under consideration, a substantial majority of 84% (N=92) comprised Non-smokers, encompassing both formerly smokers 12% (N=13) and never Smokers 72% (N=79), while 16% (N=18) were identified as current Smokers (Fig 1).

At the commencement of the study, a significant 80% (N=88) of the participants were diagnosed at stage IV, whereas the remaining patients were distributed across stage III with 4.5 % (N=5) at stage IIIA and 15.5 % (N=17) at stage IIIB and IIIC (Table 2).

Among the participants at study inclusion, 60% (N=66) received Carboplatin-based Chemotherapy, while 40% (N=44) were administered Cisplatin-based Chemotherapy as the primary treatment (Fig 2).

The median follow-up duration was 12 months. The administration of afatinib resulted in a median Progression-free Survival (PFS) of 3.7 months. Notably, significant disease control was achieved in 45% (N=50)

Table 1 — *Performance status wise distribution of patients*

Performance Status (ECOGPS)	No of patients (%)
0	35(31.8)
1	72(65.5)
2	3(2.7)

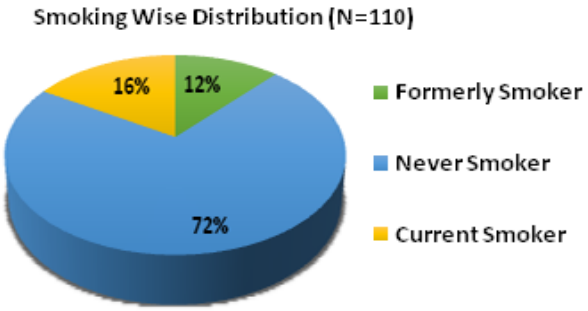


Fig 1 — Smoking status wise distribution of patients

of patients, with a few cases being deemed not evaluable (N=18). Over a median follow-up of 12 months, 2.7% (N=3) of patients exhibited complete response and 7% (N=8) demonstrated partial response, culminating in an overall disease control rate of 45% (Table 3).

Among the treatment-related adverse events observed, the most prevalent grade 2 events associated with afatinib included Diarrhea (38%), Rash/acne (32%), and stomatitis (11%). Notably, the incidence of significant grade 3 adverse events related to treatment was limited to diarrhea (7%) and Stomatitis (3%), with no notable incidence of grade 4 adverse events observed among patients treated with afatinib (Table 4).

The study's assessment of patient-reported outcomes revealed noteworthy improvements in various domains. Specifically, a considerable percentage of patients reported enhanced scores for Global Health Status/Quality of Life (31.7%), Pain reduction (36.7%), and alleviation of Cough (41.7%). Particularly significant was the proportion of patients experiencing improved Dyspnea, which amounted to 55% (Fig 3).

Discussion

The results of this study suggest that afatinib is a viable second-line treatment option for patients with advanced/metastatic Squamous Cell Carcinoma (SqCC) of the lung who have progressed after Platinum-based Chemotherapy. Afatinib showed a favorable efficacy and safety profile, as well as improved patient-reported outcomes, in this real-world setting. These findings are consistent with those of the LUX-Lung 8 trial, which was a randomized, open-label, phase III study that compared afatinib with erlotinib in patients with advanced SqCC of the lung who had progressed after at least one line of Platinum-based Chemotherapy. In that trial, afatinib significantly prolonged Progression-Free Survival (PFS) and Overall Survival (OS) compared with erlotinib with median PFS of 2.6 *versus* 1.9 months [Hazard Ratio (HR) 0.81, 95% Confidence Interval (CI) 0.69-0.95; p = 0.0077] and median OS of 7.9 *versus* 6.8 months (HR 0.81, 95% CI 0.69-0.95; p = 0.0077), respectively. Afatinib also demonstrated a higher Objective Response Rate (ORR) of 6% versus 3% (p = 0.0296) and a longer duration of response of 18.4 versus 13.1 weeks. The most common Adverse Events (AEs) associated with afatinib were Diarrhea, Rash/acne and Stomatitis, which were generally manageable with supportive care and dose adjustments.

Table 2 — *Stage wise distribution of patients*

Stage	No of patients	Percentage
IIIA	5	4.5%
IIIB	7	6.4%
IIIC	10	9.1%
IV	88	80%

Table 3 —*Tumour Response: progression free survival, objective response rate and disease control rate*

Treatment Outcome	Afatinib treated patients
Median PFS (months)	3.7
Complete Response (CR)	3 (2.7%)
Partial Response (PR)	8 (7%)
Stable Disease (SD)	39(35.3%)
Disease Progression (DP)	42(38.18%)

Table 4 — *Treatment-related adverse events*

Adverse Event (CTCAE v5.0)	Grade 2	Grade 3	Grade 4
Diarrhoea	38%	7%	<1%
Rash or acne	32%	3%	
Stomatitis	11%	2%	
Fatigue	4%	<1%	
Nausea	3%	<1%	
Decreased appetite	1%	<1%	

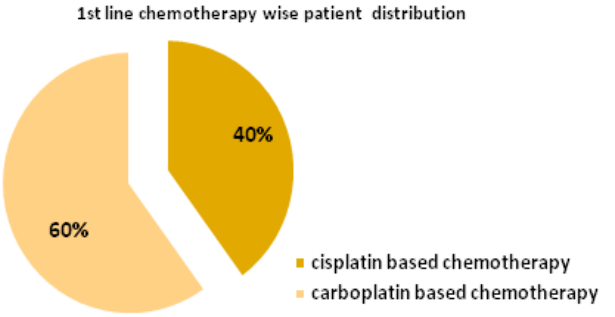


Fig 2 — 1st line treatment wise distribution of patients

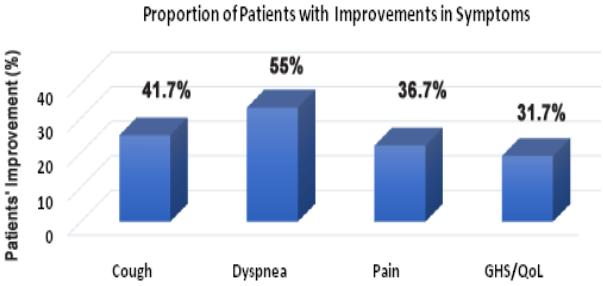


Fig 3 — Proportion of Patients showing Improvements in Symptoms

The LUX-Lung 8 trial was the first to demonstrate a survival benefit for a second-generation EGFR inhibitor over a first-generation EGFR inhibitor in patients with advanced SqCC of the lung. However, the LUX-Lung 8 trial had some limitations, such as the exclusion of patients who had received prior immunotherapy or targeted therapy the lack of biomarker analysis, and the potential selection bias due to the open-label design. Therefore, real-world data are needed to complement the results of the LUX-Lung 8 trial and to provide more evidence on the effectiveness and safety of afatinib in different patient populations and clinical settings.

The present study is one of the few real-world studies that have evaluated afatinib as a second-line treatment for advanced/metastatic SqCC of the lung. The results of this study are in line with those of the LUX-Lung 8 trial, showing that afatinib has a favorable efficacy and safety profile in this setting. The median PFS of 3.7 months observed in this study is higher than that reported in the LUX-Lung 8 trial (2.6 months), which may be attributed to the differences in patient characteristics, such as age, smoking status, ECOG PS, and prior treatment history. The ORR of 9.7% and the disease control rate of 45% observed in this study are also comparable to those reported in the LUX-Lung 8 trial (6% and 50%, respectively). The AEs associated with afatinib in this study were mostly mild to moderate and manageable with supportive care and dose adjustments, similar to those reported in the LUX-Lung 8 trial. The most common grade 2 AEs were Diarrhea (38%), Rash/acne (32%) and Stomatitis (11%), and the most common grade 3 AEs were Diarrhea (7%) and Stomatitis (3%). No grade 4 AEs or treatment-related deaths were observed in this study.

In addition to the efficacy and safety outcomes, this study also assessed the patient-reported outcomes. The results showed that afatinib improved several domains of quality of life, such as Global health status/quality of life, pain, cough, and dyspnea. These improvements are clinically meaningful and reflect the positive impact of afatinib on symptom control and functional status in patients with advanced SqCC of the lung. These findings are also consistent with those reported in a post-hoc analysis of the LUX-Lung 8 trial, which showed that afatinib significantly delayed the time to deterioration of cough and dyspnea compared with erlotinib.

Conclusions

In conclusion, this study provides real-world evidence on the effectiveness and safety of afatinib as a second-line treatment for patients with advanced/metastatic SqCC of the lung who have progressed after Platinum-based Chemotherapy in Indian patients. The results of this study are in line with those of the LUX-Lung 8 trial and support the use of afatinib in this setting. Afatinib showed a favorable efficacy and safety profile, as well as improved patient-reported outcomes, in this real-world setting. Further studies are needed to explore the potential biomarkers and mechanisms of resistance to afatinib in patients with advanced SqCC of the lung.

Limitations of the study :

- The study did not include a control arm, so it is not possible to say definitively that afatinib was responsible for the observed improvements in survival and quality of life.
- The follow-up period was relatively short, at only 12 months. This makes it difficult to assess the long-term effects.

Disclosure : The authors report no conflict of interest in this work.

Funding : There is nothing to disclose on our part and No funding received from any source for this study.

References

1 World Health Organization. (2020). Cancer. Retrieved from https://www.who.int/news-room/fact-sheets/detail/cancer
2 Squamous cell carcinoma of the lung: Molecular subtypes and therapeutic opportunities. Clinical Cancer Research: *An Official Journal of the American Association for Cancer Research* 2012; **18(9):** 2443-51.
3 Squamous cell carcinoma of the lung - Harvard Health (nd). Retrieved January 17, 2023, from https://www.health.harvard.edu/a_to_z/squamous-cell-carcinoma-of-the-lung-a-to-z
4 Acker F, Stratmann J, Aspacher L, Nguyen NTT, Wagner S, Serve H, *et al* — KRAS mutations in squamous cell carcinomas of the lung. Frontiers in Oncology, 11, 2021.
5 Frontiers | EGFR-Mutated Squamous Cell Lung Cancer and Its Association With Outcomes | Oncology
6 Sequist LV — Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31:** 3327-34.
7 Squamous Cell Carcinoma in the Lungs: What to Know - Very well Health
8 National Cancer Institute — Immunotherapy to Treat Cancer. Retrieved from https://www.cancer.gov/about-cancer/treatment/types/immunotherapy 2018.
9 KEYTRUDA® (pembrolizumab) for Advanced Non–Small Cell Lung Cancer (NSCLC).
10 Gettinger S — Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study. *J Clin Oncol* 2018; **36:** 1675-84.
11 Reck M — Docetaxel plus Nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; **15:** 143-55.
12 Hanna N — Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22:** 1589-97.
13 Afatinib (Gilotrif) | LungCancer.org
14 LUX-Lung 8: A Phase III Trial of Afatinib vs Erlotinib in Squamous Cell Carcinoma of the Lung - The ASCO Post
15 Afatinib *versus* erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial - The Lancet Oncology.

Original Article

A Prospective Observational Study on Anthropometric Correlation with Severity of Chronic Venous Disease in the Indian Population

Suyambu Raja[1], Anoop Vasudevan Pillai[2], Anjaly S Nair[3], Riju Ramachandran[4]

Background : Chronic Venous Disease (CVD) is a complex disease, common Worldwide. A paradox prevails in the prevalence of this disease in different populations. The literature regarding the disease among the Indian population is sparse.

Aims and Objectives : This study aimed to determine the correlation of anthropometry with the severity of chronic venous disease in the Indian population.

Settings and Design : This is a prospective observational study conducted on a total of 314 patients with Chronic Venous Insufficiency (CVI) in our institution, from 2018 to 2020.

Materials and Methods : The height, weight, BMI (Body Mass Index), upper segment length, lower segment length, upper: lower segment ratio of patients was taken after acquiring their demographical and clinical details. Based on visual inspection, the severity of the disease was classified using the Clinical Aetiological Anatomical Pathological (CEAP) "C" classification.

Statistical analysis used : Pearson's correlation coefficient was computed to find the relationship between anthropometric variables and the age of the first symptom.

Results : Of the 314 patients in the study, CVI with ulceration is more common among males (61.5%) with BMI<25 and skin changes were more common among females (62.5%) with BMI<25. The median age of presentation of venous symptoms is 44 years. The anthropometric variables showed a significant mild negative correlation with the age of onset of the first venous symptom.

Conclusions : Our study on Chronic Venous Disease (CVD) in the Indian population shows a divergent result when compared to the western literature.

[*J Indian Med Assoc* 2023; **121(10):** 48-51]

***Key words* : Anthropometry, Chronic Venous Disease (CVD), Venous Insufficiency, Venous Ulcer.**

Chronic Venous Disease (CVD) is a long term morphological and functional abnormality of the venous system[1]. Chronic Venous Insufficiency (CVI) is an advanced form of the disease denoting the functional abnormalities of the venous system producing edema, skin changes or ulceration[1]. Constant research existed in the domains of etiopathogenesis, epidemiological diversity, diagnosis, and treatment of venous disease since the Hippocratic era to date. The prevalence of the disease varies with BMI between males and females and has a geographical variation. Literature from western countries show increased prevalence in obese and elderly females[2,3]. There are contrasting reports of high prevalence of severe venous insufficiency among men in different parts of the World. Studies related to the prevalence of CVI and its associated risk factors in the Indian population are very few. This study aims to determine the correlation of anthropometry with the severity of CVD in Indian population. We also aim to study the variation in the epidemiological trend, severity, age of presentation of CVD in the Indian population in relation to their body physique.

Editor's Comment :

- CVD – a more common lifestyle disease of the present generation shows a variation in presentation in Indian population compared to western population.

Materials and Methods

Selection of participants :

This is a prospective observational study of all patients who presented to our department with complaints of pain, ulcer, oedema or dilated veins in the lower limbs and diagnosed with venous disease in one or both lower limbs.

Sample size - Based on the proportion of severity of Chronic Venous Disease CEAP C0 -C3 and CEAP

[1]MS, Senior Resident, Department of General Surgery, Mahatma Gandhi Medical College and Research Institute, Puducherry 607402

[2]MS, Assistant Professor, Department of General Surgery, Amrita Institute of Medical Science, Kochi, Kerala 682041

[3]MSc, Tutor, Department of Biostatistics, Amrita Institute of Medical Science, Kochi, Kerala 682041

[4]DNB, Professor, Department of General Surgery, Amrita Institute of Medical Science, Kochi, Kerala 682041 and Corresponding Author

Received on : 04/12/2021

Accepted on : 29/11/2022

C4 - C6 with respect to BMI > 25kg/m^2 (40.8%) and BMI <25kg/m^2 (23.1%) observed in an earlier publication[4] and with 80% power and 95% confidence the minimum sample size in each group comes to 108.

Ethical consideration :

The study was approved by the Ethics Committee and the Institutional Review Board (IRB) and registered with the Clinical Trial Registry, India (CTRI/2019/07/020337).

Technical information :

Informed consent was taken from all patients after explaining all the details related to the study. Demographical and clinical details regarding the age of the first venous symptom, associated co-morbidities were documented. To avoid interobserver variation the first author measured the patients' height and weight, using a standardized stadiometer and weighing scale, in all cases. The lower body segment length was measured from the pubic symphysis to the floor with the patient in a standing position. The upper body segment length was calculated by subtracting the lower body segment length from the total height. The upper segment / lower segment ratio (U/L ratio) was calculated and recorded. Body Mass Index (BMI) was calculated from the height and weight with the formula Weight (kg)/Height $(m)^2$. The severity of the disease was classified according to the CEAP "C" classification. Further details of the site, the segment of veins involved and also perforator involvement was evaluated by clinical examination and a venous duplex study of the affected limb. All the details collected were entered into an excel sheet.

Statistical analysis :

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). Categorical variables were expressed using frequency and percentage. Numerical variables were presented using mean and Standard Deviation. Chi-square test was used to find the association of Gender with BMI and CEAP C score. Independent sample t-test was used to find the difference in the mean values of all continuous clinical parameters between the two groups of CEAP scores and BMI. To find the relationship between the anthropometric variables and the age of the first symptom, Pearson's correlation co-efficient was used and its statistical significance was tested using Linear Regression t test. A p-value of <0.05 was considered to be statistically significant.

Results

The study included 314 patients with 135(43%) males and 179(57%) females. There were 225 patients (71.7%) with BMI ≥25 kg/m^2 and the remaining 89 (28.3%) had BMI < 25 kg/m^2. Based on the severity of the CVD, 131(42%) patients were included in CEAP classC1-C3 and 183(58%) in CEAP class C4-C6. On further analysis of the patients with CEAP C4-C6, we found 131(71.58%) patients had ulceration and 52(28.42%) patients had only skin change. The median age of presentation of the first venous symptom in our study population is 44 years. The demographical and clinical data are listed in Table 1.

The data analysis showed that a more severe form of CVD was seen in 142 females (63.1%) with BMI ≥25 kg/m^2 and this result was statistically significant (0.001). On further sub classifying the patients according to CEAP C class and then analyzing data of only CEAP C4- C6 category patients, the prevalence of skin changes is higher in the females with BMI < 25(62.5%) (Table 2). Ulceration was more common among the 24 males with BMI <25 (61.5%) (Table 3). The mean age of first venous symptom is around 41years in males with BMI ≥25 and females with BMI<25. However, this result did not achieve statistical significance. The anthropometric variables like height, weight, upper segment length and

Table 1 — *Demographical and clinical details*

Total number of patients		314
Age (range)		20-87
Median age of first venous symptom		44 years
Based on	Males	135
	Females	179
Based on BMI	<25	89
	≥25	225
CEAP C CLASS	CEAP C1-C3	131
	CEAP C4-C6	183
Subclassification	With ulceration	131
	Skin change only	52
Valvular incompetence	Isolated Perforator incompetence	24
	Combined incompetence	290
Comorbidity	Hypertension	49
	Diabetic	49
	Dyslipidaemia	50
	CAD	5
	Hypothyroidism	17

CEAP – Clinical Etiological Anatomical and Physiological Classification, BMI – Body Mass Index, CAD – Coronary Artery Disease

Table 2 — *Association between BMI and Gender in patients with skin change*

BMI	Gender		p-value
	Male n(%)	Female n(%)	
BMI <25 (8)	3(37.5)	5(62.5)	1.000
BMI ≥25(46)	18(39.1)	28(60.5)	

BMI – Body Mass Index

Table 3 — *Association between BMI and Gender in patients with ulceration*

BMI	Gender		p-value
	Male n(%)	Female n(%)	
BMI <25 (39)	24(61.5)	15(38.5)	0.044
BMI ≥25(90)	38(42.2)	52(57.8)	

BMI – Body Mass Index

lower segment length showed a mild negative correlation with the age of the first symptom of venous disease. When analysed we found it to be statistically significant (<0.001). Though BMI and U/L ratio showed a mild negative correlation with the age of the first symptom of venous disease, it did not reach statistical significance (Table 4).

In our series, patients with co-morbidities (Hypertension, Diabetes Mellitus, Dyslipidaemia, Coronary Artery Disease), constituting 66.7% of the cohort, had a severe form of CVD. In this set of patients, there was also an earlier mean age of onset of the symptom (41.87±13.6 years) (p=0.01).

Combined junctional and truncal reflux was more common among patients with BMI ≥25 (94.7%) with an earlier mean age of onset of venous disease (42.90± 13.6 years) (p=0.01).

Discussion

Obesity is a well-known risk factor for CVD and its association with the severity of the disease varies indifferent ethnicities of the World. Chronic venous disease is more common among elderly females[5,6]. The results from our study showed a statistically significant association of ulceration in males with a BMI of less than 25. However, in females, with a BMI less than 25, skin changes were more common. This result is in stark contrast to many of the studies published earlier showing an increased severity of venous insufficiency in obese patients[7,8]. The median age of presentation of venous symptom in our study population is 44years.In contrast to the earlier studies where the median age of presentation of the disease is above 50 years, we have a younger patient population presenting with severe disease[5,6]. Females with a BMI <25 and males with BMI ≥25 had an earlier onset of disease with the mean age of about 41 years. Variations in the lifestyle in different ethnicities and long duration of standing, prevalent in females doing household chores, may be the reason for this divergence from the western literature noticed in our Indian Population.

The anthropometric variables like height, weight, BMI, upper segment length (trunk length), lower segment length, U/L ratio showed a mild negative correlation with the age of onset of the first symptom of venous disease. Hence, in our population younger, taller individuals tend to have more severe disease. This might be due to hydrostatic pressure exerted by the column of the blood, effect of gravity, and density of blood in such individuals. A population-based study conducted in France did not find any correlation between obesity and Chronic Venous Disease and showed a statistically significant correlation between height in women and Chronic Venous Disease[9]. The height and weight greatly influence the venous hemodynamics of the extremity. As the height and weight increase, the resting pressure increases. In these patients,the post-exercise pressure drop is very negligible, which is typical of Chronic Venous Insufficiency[10]. Upper segment length (sitting height or trunk length), total height, leg length, all had a positive correlation with the increase in Blood Pressure in children and was attributed to the hydrostatic column of Blood Hypothesis[11,12]. This may explain the association of the anthropometry of the patient with venous disease.

Table 4 — *Correlation between anthropometric variables and age of first Venous symptom*

Anthropometric variable	n	r	p-value
Height	314	-0.215	<0.001
Weight	314	-0.198	<0.001
BMI	314	-0.057	0.317
Upper segment length	314	-0.169	0.003
Lower segment length	314	-0.158	0.005
U/ L ratio	314	-0.013	0.817

BMI – Body Mass Index; U/L ratio – Upper segment to lower segment ratio

Co-morbid conditions like Diabetes Mellitus, Systemic Hypertension, Dyslipidaemia, Coronary Artery Disease and Hypothyroidism is more common among patients with an early mean age of presentation (41.87±13.6 years) of venous disease in our study. These associated co-morbidities alter the lipometabolism causing inflammatory changes in the vein wall affecting the venous hemodynamics of the lower limbs[13].

There were paradoxical reports of studies relating venous incompetence and obesity. Vlajinac, *et al* have suggested that there is no significant difference in the proportion of patients with and without reflux in relation to BMI[4]. Danielsson, *et al* have reported incompetent perforators being more common in the heavier population[6]. This in contrast to the results of our study. We found a significantly increased prevalence of combined incompetence of the saphenous venous system among patients with BMI ≥25 with an early mean age of presentation.

Limitation of the study :

(1) Recall bias in patients regarding the age of the first symptom.

(2) The study was started based on the 2004 CEAP classification but in 2020 the newly revised guideline was issued. As most of the data collection was completed by that time, we could not follow the 2020 CEAP classification.

(3) The study population involved only the patients presenting to a single centre with a venous symptom.

Conclusion

Although a disparity prevails in the gender-based distribution of Chronic Venous Disease in different ethnicities with regards to BMI, we conclude that a more severe form of Chronic Venous Insufficiency is seen in females with a BMI<25 in contrast to western literature and earlier studies in Indian population. Our study on CVD in the Indian population shows a contradictory result when compared to western literature. The disease tends to occur a decade earlier in our set of patients as compared to western countries. This change in the trend of the prevalence of Chronic Venous Insufficiency may be due to the recent lifestyle changes of the population. Thinner taller women less than 40 years of age had an earlier onset and more aggressive disease course.

Source(s) of support : as a part of Postgraduate thesis.

Presentation at a meeting : Nil

Conflicting Interest (If present, give more details) : Nil

References

1 Eklof B, Perrin M, Delis KT, Rutherford RB, Gloviczki P — Updated terminology of chronic venous disorders: The VEIN-TERM transatlantic interdisciplinary consensus document. *J Vasc Surg [Internet]* 2009; **49(2):** 498-501. Available from: http://dx.doi.org/10.1016/j.jvs.2008.09.014

2 Michael H. Criqui, Maritess Jamosmos, Arnost Fronek, Julie O. Denenberg, Robert D. Langer, John Bergan BAG — Chronic Venous Disease in an Ethnically Diverse Population. *The San Diego Population Study* 2015; **158(5):** 448-56.

3 Brand FN, Dannenberg AL, Abbott RD, Kannel WB — The epidemiology of varicose veins: the Framingham Study. *Am J Prev Med* 1988; **4(2):** 96-101.

4 Vlajinac HD, Marinkovic JM, Maksimovic MZ, Matic PA, Radak DJ — Body mass index and primary chronic venous disease-A cross-sectional study. *Eur J Vasc Endovasc Surg [Internet]* 2013; **45(3):** 293-8. Available from: http://dx.doi.org/10.1016/j.ejvs.2012.12.011

5 Schaefer E, Petrini O — Chronic Venous Insufficiency in Italy: *The 24-cities Cohort Study* 2005; **429(July 2003):** 422-9.

6 Zahariev T, Anastassov V, Girov K, Goranova E, Grozdinski L, Kniajev V, *et al* — Prevalence of primary chronic venous disease: the Bulgarian experience. *Int Angiol [Internet]* 2009; **28(4):** 303-10. Available from: http://europepmc.org/abstract/MED/19648874

7 Danielsson G, Eklof B, Grandinetti A — The Influence of Obesity on Chronic Venous Disease 2002; **36(4):** 271-6.

8 Nelzén O, Bergqvist D, Lindhagen A — Venous and non-venous leg ulcers: clinical history and appearance in a population study. *Br J Surg* 1994; **81(2):** 182-7.

9 Carpentier PH, Maricq HR, Biro C, Claire O — Prevalence , risk factors , and clinical patterns of chronic venous disorders of lower limbs/ : A population-based study in France 2000; 650-9.

10 Kügler C, Strunk M, Rudofsky G — Venous pressure dynamics of the healthy human leg: Role of muscle activity, joint mobility and anthropometric factors. *J Vasc Res* 2001; **38(1):** 20-9.

11 Regnault N, Kleinman KP, Rifas-Shiman SL, Langenberg C, Lipshultz SE, Gillman MW — Components of height and blood pressure in childhood. *Int J Epidemiol* 2014; **43(1):** 149-59.

12 Zhang YX, Zhao JS, Chu ZH, Wang L Sen — The association between components of height and blood pressure among children and adolescents in Shandong, China. *Int J Cardiol [Internet]* 2015; **182(C):** 18-9. Available from: http://dx.doi.org/10.1016/j.ijcard.2015.01.008

13 Göstl K, Obermayer A, Hirschl M — Pathogenesis of chronic venous insufficiency by obesity: Current data and hypotheses. *Phlebologie* 2009; **38:** 108-13.

Review Article

Management of Steroid-induced Hyperglycemia

Subhodip Pramanik[1], Sayantan Ray[2], Kaushik Biswas[3], Tapas Bandyopadhyay[4], Madhusha Mukhopadhyay[5]

Glucocorticoids or steroids are widely used across many medical specialties because of their anti-inflammatory and immunosuppressive effects. Although widely prescribed Glucocorticoids (GC) have many adverse effects and hyperglycemia is one of the most common and best known. The use of GC in patients with diabetes will worsen hyperglycemia, and will warrant temporary additional and more active, glycemic management. GCs may also precipitate new-onset hyperglycemia in non-diabetic patients and this may be termed 'steroid-induced diabetes'. However, there is a lack of quality studies to determine specific strategies about the management of people with steroid-induced hyperglycemia. In this article, we discuss the important epidemiologic characteristics related with steroid use, highlighting on identification of high-risk populations. In addition, the pathophysiology has been discussed in detail, focusing on various patterns of hyperglycemia induced by the different formulations and provide diagnostic clues based on treatment duration and the administration schedule of GCs. Finally, a treatment strategy is suggested based on current evidence and understanding of the mechanism of action of both, the different types of GCs and the therapeutic options in ambulatory and hospital settings.

[*J Indian Med Assoc* 2023; **121(10):** 52-6]

Key words **: Glucocorticoids, steroid-induced hyperglycemia, diabetes, pathophysiology. treatment strategy.**

Glucocorticoids (GC) are widely used for anti-inflammatory and immunosuppressive purposes[1]. In current era, it is one of the established treatment strategies of SARS-CoV2 (COVID-19) pneumonia[2]. The rationale for dexamethasone in severe infection is that the damage caused by the disease is strongly related to the hyperactive inflammatory response triggered. However, GCs are burdened by several metabolic adverse effects including hypertension, diabetes and osteoporosis[3]. Steroids not only exacerbate hyperglycemia in diabetic patients but also cause new-onset Diabetes Mellitus (DM)[4]. Among hospitalized patients, Steroid-induced Hyperglycemia (SIH) can be seen in nearly 50% patients with as much as 68% increase in blood sugar levels[5]. Diabetic Ketoacidosis (DKA) and non-ketotic hyperosmolar state have also been reported[6].

Steroid-induced Diabetes Mellitus (SIDM) is classically defined as an abnormal increase in Blood Glucose (BG) concentration during GC use without a prior history of diabetes[6]. As per American Diabetes Association (ADA) criteria, diabetes is defined when an 8-h fasting BG ≥126mg/dL, 2-h post-75g Oral Glucose Tolerance Test (OGTT) ≥200mg/dL, a glycated hemoglobin (HbA1c) value ≥6.5% or a random plasma BG value ≥200mg/dL during hyperglycemia or hyperglycemic crisis[7]. But SIDM is underdiagnosed since classical criteria are not so sensitive because GCs preferentially increase Postprandial Plasma Glucose (PPPG)[8].

Editor's Comment :

- SIDM and SIH are commonly encountered problems in the clinical practice, but there is inadequate information and a lack of scientific evidence as to the clinical diagnosis and treatment. Screening for SIDM is suggested in all patients treated with medium to high doses of GCs. Early and precise diagnosis of SIDM and/or identification of SIH must rely on 2-h postprandial glycemia. While choosing between Oral hypoglycemic drugs and insulin, the latter should have always to be preferred, especially for hospitalized patients.
- Even after nearly 70 years of using GCs , many questions are unanswered regarding GC-induced hyperglycemia. Factor identification causing variability in the insulin response in hospitalized patients with SIDM/SIH is needed to improve patient management. In out-patients on long-term steroid, further understanding of the CV risk associated with post-prandial hyperglycemia is of paramount importance.

Epidemiology :

GC-induced hyperglycemia is around 12% in elderly but the prevalence is still unknown[9]. The incidence of

[1]MD, DM, Consultant, Department of Internal Medicine, Neotia Getwel Multispecialty Hospital, Siliguri, West Bengal 734010

[2]MD, DM, Assistant Professor, Department of Internal Medicine, AIIMS, Bhubaneswar, Odisha 751019

[3]MD, DM, Senior Consultant, Department of Endocrinology, Medica Superspecialty Hospital, Kolkata 700099

[4]MD, FICP, Senior Consultant, Department of Internal Medicine, Medica Superspecialty Hospital, Kolkata 700099 and Corresponding Author

[5]MBBS, DNB, MRCP, Consultant, Department of Internal Medicine, Medica Superspecialty Hospital, Kolkata 700099

Received on : 03/10/2022

Accepted on : 28/10/2023

GC-induced hyperglycemia and diabetes in non-diabetic people were 32.3% and 18.6%, respectively[10]. However, not all patients who use GC develop SIDM, suggesting that SIDM occurs only in vulnerable populations[11,12]. Oral GCs are associated with diabetes in 2% cases and GC-containing topical preparations, inhalers, eye drops or injections are minimally associated with diabetes[13]. In hospital, SIDM with high dose prednisolone has a rapid onset with a peak in the late afternoon needing early BG monitoring[14,15].

Risk Factors — Patient and Steroid Specific :

The main steroid-related risk factors (Table 1) for SIDM/SIH are: the steroid type and dose, odds ratio (OR) (OR:1.01, 95%CI:0.996-1.018)[16], duration of treatment[5] and a continuous GC scheme (OR:2.0, 95%CI:1.29-3.1)[17]. The rise in BG is most often postprandial and dependent on the steroid type: short acting (hydrocortisone), intermediate- acting (prednisone and methylprednisolone) and long-acting (dexamethasone). In addition, there are patient-specific risk factors such as older age (OR:1.05, 95%CI:1.02-1.09)[18], HbA1c, BMI (OR:2.15, 95%CI:1.12-4.13)[19], gestational DM, positive family history (OR:10.29, 95%CI:2.33-45.54), mycophenolate mofetil [OR:4.80, 95%CI:1.32-17(0.04)5] and/or calcineurin inhibitors[20].

Table 1 — *Risk Factors for Glucocorticoid-Induced Diabetes Mellitus*

■ Higher dose of glucocorticoid treatment (prednisolone >20 mg, hydrocortisone >50 mg, dexamethasone >4 mg)
■ Longer duration of glucocorticoid treatment
■ Advanced age
■ High body mass index
■ Previous glucose intolerance or impaired glucose tolerance
■ Personal history of gestational diabetes or previous glucocorticoid-induced hyperglycemia
■ Family history of diabetes mellitus
■ Hemoglobin A1c ≥6%

Adapted from Suh S, Park MK — Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. *Endocrinology and Metabolism* 2017; **32(2):** 180.

Pathophysiology :

The precise mechanisms accounting for GC effects on glucose homeostasis are still incompletely understood. Firstly, as much as 60-80% of increase in Insulin Resistance (IR) can be observed[19]. Steroids can affect the GLUT-4 transporter related signaling pathways leading to 30-50% decrease in glucose uptake in muscle cells[21]. This can also be affected by increase in serum free fatty acids and amino acids caused by catabolism of lipids and proteins due to steroids. IR is also directly increased by induction of nuclear Peroxisome Proliferator-activated Receptor alpha (PPAR-α)[22]. Intramuscular glucose entry and storage is also reduced by lipid accumulation in the muscles, promoted by steroids. Steroids can enhance the effects of glucagon and epinephrine through gluconeogenesis. They also inhibit the synthesis and secretion of insulin through lipotoxicity by causing a decrease in GLUT-2 and glucokinase receptor expression. Table 2 summarises the putative mechanisms associated with SIDM.

Table 2 — *Pathophysiology of corticosteroid-induced hyperglycemia*

Increase in insulin resistance with increased glucose production and inhibition of the production and secretion of insulin by pancreatic β-cells
➢ Corticosteroids increase endogenous glucose production, increment in gluconeogenesis and antagonizing the metabolic actions of insulin
➢ Enhance the effects of other counterregulatory hormones, such as glucagon and epinephrine, which increase the endogenous synthesis of glucose
➢ Also been shown that the expression of the nuclear receptor peroxisome proliferator-activated receptor a is necessary for the increment in endogenous gluucose production induced by corticosteroids
➢ Corticosteroids reduce peripheral glucose uptake at the level of the muscle and adipose tissue
➢ Costicosteroids also inhibit the production and secretion of insulin from pancreatic ß-cells and induce ß-cell failure indirectly by lipotoxicity

Adapted from : Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL — Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. *World Journal of Diabetes* 2015; **6(8):** 1073.

Effects of SIH :

Despite the wide prevalence, the effect of chronic SIH on other medical conditions and in particular, mortality is not well established. It has been associated with cardiovascular risk due to its association with increased LDL, activation of coagulation cascade, endothelial dysfunction, increased cytokines and oxidative stress[23]. Poor wound healing, increased length of stay, recurrent re-admissions, increased risk of infection and higher overall mortality are some of the risks associated with SIDM compared to T2DM[24,25]. A 2-3 times higher risk of graft failure and cardiovascular events is observed in kidney transplant recipients with SIDM[26].

Diagnosis :

All patients receiving GC therapy should be evaluated for hyperglycemia. The established criteria for the diagnosis of diabetes provides a low diagnostic sensitivity in the majority of patients with SIDM[7,27].

Therefore, the diagnosis of SIDM in most patients has been consistently suggested on the basis of the 2-hours postprandial glucose 200mg/dL. The postlunch glucose level has the maximum diagnostic sensitivity, especially for the single morning dose administration of intermediate-acting GCs[3]. In people with pre-existing DM at risk of T2DM, screening is indicated even with low doses of GC. Current recommendations include initiating Point-of-Care (POC) testing in any hospitalized patient being treated with GCs[15].

Treatment :

Therapeutic goals and considerations :

With regard to the diagnostic criteria, current glycemic thresholds for hospitalized, non-critically ill, patients are usually accepted[28]. From a practical viewpoint, the treatment for SIDM and SIH should be started when the preprandial and postprandial BG values are ≥140mg/dL and ≥200mg/dL respectively[3]. In the case of chronic GC treatment, the control goals and need for treatment are based on recommended control target. Consequently, the choice among Oral Antidiabetic Drugs (OADs) or insulin is a crucial step, which should consider also the duration of the GC therapy[29].

Treatment of SIDM :

Once-daily steroid treatment Non-insulin therapies —

Non-insulin Therapies — The use of OAD is advocated in the treatment of mild GC-induced hyperglycemia without a prior known history of DM[3]. In the Joint British Diabetes Societies (JBDS) guidelines, gliclazide is recommended[30]. However, sulphonylureas may cause hypoglycaemia due to long duration of action[31,32]. Repaglinide has an immediate onset of action and a short half-life, better adapting to the GC-induced post-prandial hyperglycemia and has a low risk of hypoglycaemia. Evidence for using thiazolidinediones in patients with SIDM is weak[33]. For low-dose GC, metformin is a logical choice if renal function is adequate[34-36]. Seelig, *et al* demonstrated that preventive metformin treatment was effective in patients without diabetes receiving GC treatment with regard to glycemic control, even after adjustment for gender, total GC dose and HbA1c[35]. However, transient SIH is not ideally treated by pioglitazone and metformin owing to their slow onset of action. Concomitant treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor can improve pancreatic islet-cell function in patients getting high-dose prednisolone but failed to prevent worsening of glucose tolerance by GC treatment[37]. In a study on patients with acute exacerbation of COPD, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor dapagliflozin did not offer a better glycemic control of hyperglycemia induced by prednisolone compared to placebo[38]. Results from a recent study comparing empagliflozin to isophane insulin in individuals with SIDM are pending[39].

Insulin Therapies — For those requiring a single daily dose of steroid, a preferred option may be weight-based Neutral Protamine Hagedorn (NPH) insulin once daily at the same time as the steroid. Its onset, peak effect and duration of action closely matches the pattern of hyperglycemia induced by intermediate-acting GCs[19]. The JBDS guidelines advocate the initiation of 10 U of human basal insulin, with a daily dose increment of 10-20%, titrated to the BG level[30]. Basal analogue insulin such as glargine can be used if hyperglycemia persists through the day and extends into the evening. However, insulin NPH has the potential to treat daytime hyperglycemia better and avoid overnight and early morning hypoglycemia arising from longer-acting formulations.

Multiple steroid doses —

Multiple doses of oral or intravenous steroids can cause hyperglycemia around the clock. A sliding scale or Multiple Daily Injection (MDI) using subcutaneous insulin is the most suitable choice for most patients[30]. For those receiving twice-daily prednisolone or dexamethasone, it may be appropriate to substitute insulin glargine or detemir for NPH insulin. For Post-prandial elevations of BG, longer-acting basal insulin can be used alone or as combination treatment with short-acting insulin[40].

Treatment of SIH :

Type 2 Diabetes —

For those using insulin secretagogues, the morning dose should be increased. In the JBDS guidelines, a 40mg increment in gliclazide dose to a maximum dose of 240mg is recommended[30]. Temporary addition of insulin NPH in the morning or changing of metformin dosage may be considered.

If the person is on basal insulin only, consider switching to morning administration and increase dose in 10% increments every 24-48 hours, corresponding to the results of BG monitoring. For those using a twice-daily pre-mixed insulin regimen, a 10% increase in the morning insulin dose should be considered every 24-48 hours[30]. For those using an MDI regimen, an increment in short-acting insulin dose in lunch and evenings may be warranted.

Type 1 Diabetes —

The insulin dose must be titrated to maintain

glucose to target BG levels. Often, the lunch and evening short acting boluses may need to be increased if a basal bolus regimen is utilized. For those using a twice-daily pre-mixed insulin regimen, the morning insulin dose usually needs to increase by 10% daily[30].

SIH/SIDM in admitted patients :

The Endocrine Society Clinical Practice Guidelines (ESCPG) recommends an initial daily insulin dose of 0.3-0.5 units/kg in hospitalized patients with hyperglycemia on GCs[15]. Others have recommended to commence weight-based NPH insulin at 0.1U/kg for every 10mg of prednisone up to a maximum of 0.4U/kg[19]. Radhakuty and Burt recommended a starting daily dose of 0.5U/kg in hospitalized patients, if they have not received insulin previously, for rapid glycemic control. Those at higher risk of hypoglycemia should receive an initial lower dose, such as 0.3-0.4U/kg[40].

In general, when considering insulin therapy, either weight-based or total daily dose based regimen can be started. The correctional doses of insulin can be adjusted according to the scale as provided in Table 3. However, individual variations in response to insulin is expected and CBG monitoring (4-6 hourly) is required. In the setting of COVID-19 and unprecedented use of steroids, there can be acute metabolic decompensation for which intravenous insulin therapy may be warranted.

Table 3 — *Correctional scale of rapid/short acting insulin*

BG (mg/dl)	Insulin sensitive TDD<50 U BW< 50 KG	Usual TDD 50-100 U BW 50-100 KG	Insulin resistant TDD > 100 BW >100 KG
141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

Insulin sensitive : Older, lean, T1DM, CKD or CLD / Insulin-resistant: Obese or on Glucocorticoids

All hospitalized patiens receiving insulin for SIH/SIDM must be advised regarding the possibility of hypoglycemia during the stopping or tapering of insulin. Current practice is to taper the prednisolone and insulin proportionately[19]. Patients who have prior good glycemic control, can be advised to resume their usual treatment even if a high-dose steroid is stopped abruptly[40].

Conclusion and Future Directions :

SIDM and SIH are commonly encountered problems in the clinical practice, but there is inadequate information in the literature and a lack of scientific evidence as to the clinical connotations of GC-induced hyperglycemia and strategies for its diagnosis and treatment. Screening for SIDM is suggested in all patients treated with medium to high doses of GCs. The main caveat lies on the early and precise diagnosis of SIDM and/or identification of SIH, which must rely on 2-hours Post-prandial glycemia. While choosing between OADs and insulin, the latter should have always to be preferred, especially for hospitalized patients. Based on present evidence, a weight-based NPH insulin regimen is advocated as first-line therapy for SIDM/SIH in such patients.

Even after nearly 70 years of using GCs to treat various diseases, many questions are unanswered regarding GC-induced hyperglycemia. Factor identification causing variability in the insulin response in hospitalized patients with SIDM/SIH is needed to improve patient management. In outpatients on long-term steroid, further understanding of the CV risk associated with Post-prandial hyperglycemia and studies of effects of glucose-lowering treatments are required for a stronger evidence base regarding management of this large group of patients.

References

1 Hoes JN, Jacobs JW, Buttgereit F, Bijlsma JW. Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis. *Nature reviews Rheumatology* 2010; **6:** 693-702.

2 Iwabuchi K, Yoshie K, Kurakami Y, Takahashi K, Kato, Y, Morishima T — Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: report of three cases. *J Infect Chemother* 2020; **26:** 625-32.

3 Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Minambres I, Gomez-Huelgas R — Glucocorticoid-induced hyperglycemia. *J Diabetes* 2014; **6:** 9-20.

4 Trence DL — Management of patients on chronic glucocorticoid therapy: an endocrine perspective. *Prim Care* 2003; **30:** 593-605.

5 Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA — Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract 2006;* **12:** 358-62.

6 Caðdaþ DN, Paç FA, Cakal E — Glucocorticoid-induced diabetic ketoacidosis in acute rheumatic fever. *J Cardiovasc Pharmacol Ther* 2008; **13:** 298-300.

7 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; **43(Suppl 1):** S14-31.

8 Iwamoto T, Kagawa Y, Naito Y, Kuzuhara S, Kojima M — Steroid-induced diabetes mellitus and related risk factors in patients with neurologic diseases. *Pharmacotherapy* 2004; **24:** 508-14.

9 Blackburn D, Hux J, Mamdani M — Quantification of the risk of corticosteroid-induced diabetes mellitus among the elder-ly. *J Gen Intern Med* 2002; **17:** 717-20.

10 Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM — Hy-perglycemia induced by glucocorticoids in nondiabetic pa-tients: a meta-analysis. *Ann NutrMetab* 2014; **65:** 324-32.

11 Kwon S, Hermayer KL — Glucocorticoid-induced hypergly-cemia. *Am J Med Sci* 2013; **345:** 274-7.

12 Healy SJ, Nagaraja HN, Alwan D, Dungan KM — Prevalence, predictors, and outcomes ofsteroid-induced hyperglycemia in hospitalized patients with hematologic malignancies. *Endocrine* 2017; **56:** 90-7.
13 Gulliford MC, Charlton J, Latinovic R — Risk of diabetes associated with prescribed glucocorticoids in a large population. *Diabetes Care* 2006; **29:** 2728-2729.
14 Fong AC, Cheung NW — The high incidence of steroid-induced hyperglycaemia in hospital. *Diabetes Res Clin Pract* 2013; **99:** 277-80.
15 Umpierrez GE, Hellman R, Korytkowski MT — Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012; **97:** 16-38.
16 Abdelmannan D, Tahboub R, Genuth S, Ismail-Beigi F — Effect of dexamethasone on oral glucose tolerance in healthy adults. *Endocr Pract* 2010; **16:** 770-7.
17 Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, Gomez-Almaguer D, Lavalle-Gonzalez FJ, Tamez-Perez HE, *et al* — Hyperglycemia related to high-dose GC use in noncritically ill patients. *Diabetol Metab Syndr* 2013; **5:** 18.
18 Kim SY, Yoo CG, Lee CT, Chung HS, Kim YW, Han SK, Shim, YS, et al — Incidence and risk factors of steroid-induced diabetesin patients with respiratory disease. *J Korean Med Sci* 2011; **26:** 264-7.
19 Clore JN, Thurby-Hay L — Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009; **15:** 469-74.
20 Mazzantini M, Torre C, Miccoli M, Baggiani A, Talarico R, Bombardieri S, Di Munno O — Adverse events during longterm low-dose glucocorticoid treatment of polymyalgia rheumatica: a retrospective study. *J Rheumatol* 2012; **39:** 552-7.
21 Ruzzin J, Wagman AS, Jensen J — Glucocorticoid-induced insulin resistance in skeletal muscles: defects in insulin signalling and the effects of a selective glycogen synthase kinase-3 inhibitor. *Diabetologia* 2005; **48:** 2119-30.
22 van Raalte DH, Ouwens DM, Diamant M — Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 2009; **39:** 81-93.
23 Perez HE, Gómez de Ossio MD, Quintanilla Flore DL, Hernández Coria MI, Tamez Peña AL, Cuz Pérez GJ, *et al* — Glucose disturbances in non-diabetic patients receiving acute treatment with methylprednisolone pulses. *Rev Assoc Med Bras* 2012; **58:** 125-8.
24 Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE — Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; **87:** 978-82.
25 Hwang JL, Weiss RE — Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes Metab Res Rev* 2014; **30:** 96-102.
26 Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, *et al* — The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006; **69:** 588-95.
27 Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S, *et al* — Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. *Nephron Clin Pract* 2007; **105:** c54-7.
28 American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; **43(Supplement 1):** S193-S202.
29 Bonaventura A, Montecucco F — Steroid-induced hyperglycemia: An underdiagnosed problem or clinical inertia? A narrative review. *Diabetes Res Clin Pract* 2018; **139:** 203-20.
30 Roberts A, James J, Dhatariya K — on behalf of the Joint British Diabetes Societies (JBDS) for Inpatient Care (2018). Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. *Diabet Med* 2018; **35:** 1011-1017.
31 Wallace MD, Metzger NL — Optimizing the Treatment of Steroid-Induced Hyperglycemia. *Ann Pharmacother* 2018; **52:** 86-90.
32 Vidler J, Rogers C, Yallop D, Devereux S, Wellving E, Stewart O, *et al* — Outpatient management of steroid-induced hyperglycaemia and steroid-induced diabetes in people with lymphoproliferative disorders treated with intermittent high dose steroids. *J Clin Transl Endocrinol* 2017; **9:** 18-20.
33 Willi SM, Kennedy A, Brant BP, Wallace P, Rogers NL, Garvey WT — Effective use of thiazolidinediones for the treatment of glucocorticoid-induced diabetes. *Diabetes Res Clin Pract* **58:** 87-96.
34 Radhakutty A, Burt MG — Management of endocrine disease: critical review of the evidence underlying management of glucocorticoid-induced hyperglycaemia. *Eur J Endocrinol* 2018; **179:** R207-18.
35 Seelig E, Meyer S, Timper K, Nigro N, Bally M, Pernicova I, *et al* — Metformin prevents metabolic side effects during systemic glucocorticoid treatment. *Eur J Endocrinol* 2017; **176:** 349-58.
36 Ochola LA, Nyamu DG, Guantai EM, Weru IW — Metformin's effectiveness in preventing prednisone-induced hyperglycemia in hematological cancers. *J Oncol Pharm Pract* 2020; **26:** 823-34.
37 van Genugten RE, van Raalte DH, Muskiet MH, Heymans MW, Pouwels PJ, Ouwens DM, *et al* — Does dipeptidyl peptidase-4 inhibition prevent the diabetogenic effects of glucocorticoids in men with the metabolic syndrome? A randomized controlled trial. *Eur J Endocrinol* 2014; **170:** 429-39.
38 Gerards MC, Venema GE, Patberg KW, Kross M, Potter van Loon BJ, Hageman IMG, *et al* — Dapagliflozin for prednisone-induced hyperglycaemia in acute exacerbation of chronic obstructive pulmonary disease. *Diabetes Obes Metab 2018;* **20:** 1306-10.
39 Klarskov CK, Holm Schultz H, Persson F, Christensen TM, Almdal TP, Snorgaard O — Study rationale and design of the EANITIATE study (EmpAgliflozin compared to NPH Insulin for sTeroIddiAbeTEs): a randomized, controlled, multicenter trial of safety and efficacy of treatment with empagliflozin compared with NPH-insulin in patients with newly onset diabetes following initiation of glucocorticoid treatment. *BMC Endocr Disord* 2020; **20:** 86.
40 Radhakutty A, Stranks JL, Mangelsdorf BL, Drake SM, Roberts GW, Zimmermann AT, Stranks SN, *et al* — Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized, controlled study. *Diabetes Obes Metab* 2017; **19:** 571-8.

Case Report

Topical Timolol Drops in the Management of Pyogenic Granuloma of Lip

Rajkiran Takharya[1], Divya Mani[2], Jude Ernest Dileep[3], Damayandhi Kaliyaperumal[4]

Pyogenic Granulomas (PG) are common benign vascular tumors of skin and mucous membrane which commonly presents in children and young adults. Clinically PG presents as friable, erythematous papule or nodule located on the head and upper extremities with a tendency to rapidly grow and bleed with minor trauma. Usually, PGs are treated with surgical excision. Here we report a case where topical application of 0.5% timolol drops led to complete resolution of PG of lower lip in a young adult with no recurrence at 3 months.

[*J Indian Med Assoc* 2023; **121(10):** 57-8]

Key words **: Topical timolol, Pyogenic Granuloma.**

Pyogenic Granulomas (PG) are common benign vascular tumors of skin and mucous membrane which commonly presents in children and young adults[1]. Usually, PGs are treated with surgical excision. Here we report a case where topical application of 0.5% timolol drops led to complete resolution of PG of lower lip in a young adult with no recurrence at 3 months.

Case Report

A 13-year-old girl presented with history of an elevated lesion over the lower lip for the past 6 months which bleeds on minor trauma (eating, brushing teeth). On examination, a single well defined erythematous crusted nodule with a collarette scale of 1.1 x 1.2 cm was seen over the lower lip. Clinical diagnosis of PG was considered and planned electrosurgical excision after a week. Meanwhile, patient was started on 0.5% timolol drops (2 drops thrice daily) which was applied over the lip, to reduce the bleeding during the excision. On review at 15 days, surprisingly the lesion was found to be resolving with marked reduction in size. Excision was deferred and timolol drops was continued for 8 weeks and at the end of eight weeks there was complete resolution of the lesion. Patient was reviewed monthly once, for a period of 3 months and found to have no recurrence (Figs 1-3).

Discussion

PG is a commonly occurring benign vascular tumor. They are commonly seen in skin and mucous membranes following trauma but can also be associated with the use of medications (oral contraceptives, isotretinoin, propyl thiouracil, etc), congenital syndromes (PASH syndrome, PAPA syndrome, PAPASH syndrome, etc), and hormonal changes like in pregnancy. Clinically PG presents as friable, erythematous papule or nodule located on the head and upper extremities with a tendency to rapidly grow and bleed with minor trauma.

Histologically, there is proliferation of capillaries with plump endothelial cells separated into lobules by a fibro myxoid stroma. Occasionally, a thicker blood vessel can be seen at the base of the lesion. Many PGs resolve spontaneously. But some may destruct the local area and produce morbidity due to disfigurement and bleeding. Many therapeutic options are available[2]. Conventionally PGs are treated by surgical excision, electrodesiccation, cryotherapy and ablative or vascular lasers. But the potential complications include pain, scarring and dyspigmentation.

Despite the high clearance rate, surgical excision may not be the preferred treatment modality in some patients, such as children and those with keloidal tendencies. Surgical intervention can worsen PG through pathergy, and similar to surgical debridement, topical debriding agents are partially contraindicated[3]. Non-surgical treatments for PG, including imiquimod, bleomycin, ingenol mebutate cream, phenol, topical beta-blockers (timolol 0.5% and propranolol 1%) and silver nitrate. Propranolol, a non-selective beta-adrenergic receptor blocker, is the first-line oral therapy for complicated infantile hemangiomas. Wine Lee, *et al* were the first to use timolol 0.5% (twice daily) on 7 children with PGs (6 cutaneous, 1 mucosal). There was variability in the time of response to therapy, although all showed at least a partial response within 2 months[4].

Editor's Comment :

- Topical timolol drops can be used to reduce the vascularity of pyogenic granuloma and it can be considered as one of the treatment option for smaller lesion.

[1]MD, Senior Resident, Department of Dermatology, Manipal Tata Medical College, Jharkhand 831017

[2]MD, Final Year Postgraduate, Department of Dermatology, Aarupadai Veedu Medical College & Hospital, Puducherry 607402

[3]MD, Assistant Professor, Department of Dermatology, Aarupadai Veedu Medical College & Hospital, Puducherry 607402

[4]MD, Associate Professor, Department of Dermatology, Aarupadai Veedu Medical College & Hospital, Puducherry 607402 and Corresponding Author

Received on : 17/01/2022

Accepted on : 26/06/2023

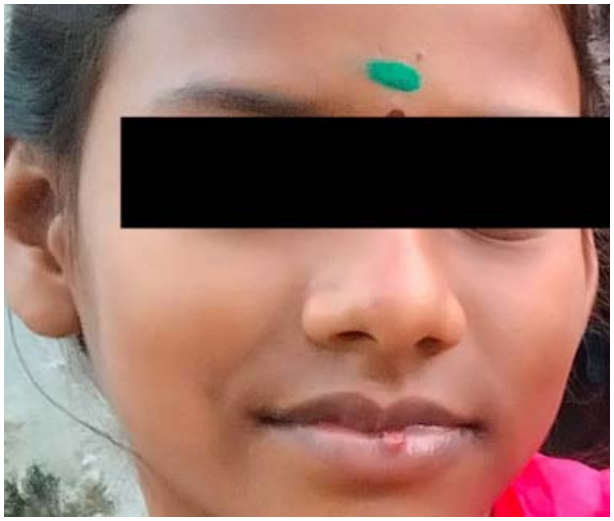


Fig 1 — Pyogenic Granuloma over lower lip before treatment

The most recent study by Gupta, *et al* reported 10 patients with PG who were treated with timolol 0.5% solution (applied 4 times a day). Four patients showed a complete response within 3-24 days, with no recurrence at 3-month follow-up. Three patients had a partial response and the remaining 3 did not respond to therapy[5]. For PG in lip, topical timolol drops use has been rarely reported in children, with favorable results. The utility of topical timolol gel (0.5%) in the treatment of PG in children has been reported. As illustrated by this case, Timolol eye drops (0.5%) could prove to be a less expensive yet effective alternative in the treatment of PG in resource limited settings. Topical timolol drops prove to be a safe modality for treatment for PG particularly in face and lip areas as pointed out in literature. Large scale studies are needed to explore the efficacy of topical timolol as monotherapy in the treatment of PG.

Conclusion

Topical timolol in the form of drops could serve as an effective, safe and less expensive modality in the treatment of mucosal PGs, as shown by our case report.

References

1 Wollina U, Langner D, Franasa K — Pyogenic granuloma - a common benign vascular tumor with variable clinical presentation: new findings and treatment options. *Open Access Maced J Med Sci* 2017; **5(4):** 423-26.

2 Plachouri KM, Georgiou S — Therapeutic approaches to pyogenic granuloma: an updated review. *Int J Dermatol* 2018 Oct 21.

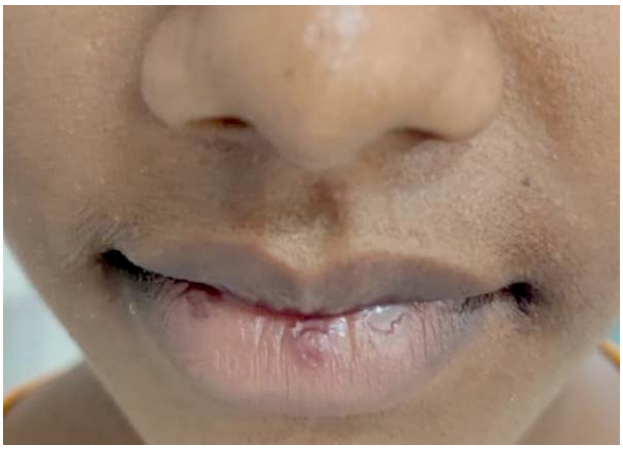


Fig 2 — Pyogenic Granuloma after 15 days of treatment

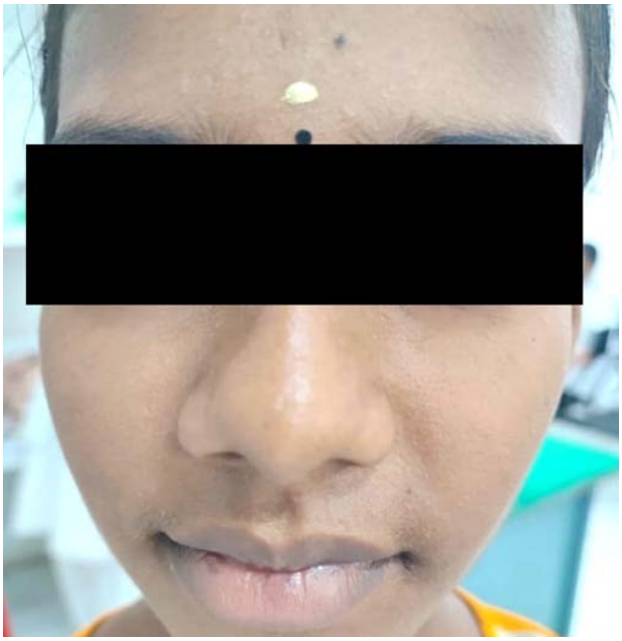


Fig 3 — Pyogenic Granuloma after 1.5 months of treatment

3 Gameiro A, Pereira N, Cardoso JC, Gonçalo M — Clinical, Cosmetic and Investigational Dermatology 2015: **8:** 285-93.

4 Wine Lee L — Treatment of pediatric pyogenic granulomas using b-adrenergic receptor antagonists. *Pediatr Dermatol* 2014; **31:** 203-7.

5 Gupta D — Is timolol an effective treatment for pyoderma gangrenosum. *Int J Dermatol* 2016; **55:** 592-5.

Case Report

Post COVID Central Retinal Vein Occlusion in a Young Woman with Well-controlled Diabetes

Rajesh K P[1]

Central Retinal Vein Occlusion (CRVO) is one among the many causes leading to high degree of visual impairment and blindness in the adult population. There is a likelihood of overlooking Cardiovascular complications when the patient is young and the diabetes is well controlled. Here we present a case of unilateral CRVO in a young lady who has well-controlled Type 2 Diabetes and a history of COVID 3 weeks back. This is to report the possibility of the occurrence of CRVO even in a patient with well-controlled Diabetes in the Post COVID phase and to keep in mind the differential diagnosis of sudden unilateral visual loss.

[*J Indian Med Assoc* 2023; **121(10):** 59-61]

Key words **: Young Diabetes, Central Retinal Vein Occlusion (CRVO), Post COVID, Hypercoagulability.**

The global prevalence of diabetes was estimated to be 9.3% (463 million people) in 2019, increasing to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. Retinal Vein Occlusion (RVO) occurs infrequently in patients with diabetes. Although the etiology is not clear, it could be related to other microvascular complications and diabetes could be taken as a risk factor for RVO[1].

Central Retinal Vein Occlusion (CRVO) is commonly associated with atherosclerotic risk factors like diabetes, hypertension and age >55 years; other associations being chronic glaucoma, hyper viscosity, coagulopathy and migraine[2]. The exact reason for occlusion of the retinal vein is often not clear. There may be a severe loss of vision but the onset is typically subacute. When venous stasis is severe, it may lead to infarction due to slowed renal arterial blood flow.

Thromboembolic complications are known to occur in COVID-19. The prevalence of venous thromboembolic events in critically ill COVID patients has been found to be high. Retinal microangiopathic changes have been observed but it is not clear if these are due to prolonged hypoxemia or are related to a more direct viral etiology[3]. Though no large-scale studies have been performed to establish the causal relationship, several cases of CRVO have been reported in COVID[4]. A panel of blood tests are usually done in individuals younger than 56 years with newly diagnosed venous occlusion[5], as younger patients are more likely to have an identifiable cause for their hypercoagulability[6].

Case Report

A 45-year-old Asian Indian female presented to the diabetic clinic with history of loss of vision in her left eye for last 2 days. She was diagnosed to have Type 2 Diabetes Mellitus (Type 2 DM) 4 years back from our clinic and she has been under regular follow up since then. She was a college lecturer and was meticulous in her diet and exercise and almost fully compliant with her medications. She was on a combination of vildagliptin + metformin (50 + 500) twice daily and had a good glycemic control. Her blood values done 1 week back were FBS 99mg/dl, 2 hours PPBS 168mg/dl and HbA1C 6.9. She was not overweight and had a BMI of 21. She was normotensive and there was no dyslipidaemia. She did not have any addictions.

Editor's Comment :

- COVID-19 has been known to cause thrombotic events.
- This case highlights the importance of recognizing CRVO as an important complication of COVID.
- Treating Physicians should not overlook this possibility even in the absence of traditional risk factors.

Vital signs on presentation –

Pulse	- 72 bpm regular
BP	-120/82 mm of Hg
Respiratory rate	-16 breaths/minute
Temperature	- 97° F Afebrile

Physical examination was unremarkable. Cardiovascular system examination was normal and there was no focal neurological deficit.

ECG showed sinus rhythm and blood sugar at presentation Random Blood Sugar (RBS) was 156 mg/dl.

Differential diagnosis considered were Branch Retinal Vein Occlusion (BRVO), CRVO, Branch Retinal Artery Occlusion, Central Retinal Artery Occlusion, Papillitis, Vitreous Haemorrhage and Retinal Detachment.

An emergency Ophthalmology consultation was sent, and a detailed Ophthalmology evaluation was done.

Ophthalmologic evaluation demonstrated a best corrected visual acuity of 6/9 in left eye and 6/6 in right eye. Pupil examination revealed a sluggishly reactive pupil on the left side and a normally reactive right pupil. There

[1]MD, DNB, MRCP, FRCP, Consultant, Department of Internal Medicine and Diabetology, KIMS Trust Hospital, Calicut 673571, PVS Hospital, Calicut 673002, Kerala and Corresponding Author

Received on : 17/08/2022
Accepted on : 21/01/2023

was no evidence of Relative Afferent Pupillary Defect (RAPD).

The intraocular pressure was 16mmHg in the left eye, and in the right, it was 14 mmHg.

A Slit lamp examination revealed normal anterior segments with open angles on both sides.

Fundus evaluation of left eye showed disc oedema, dilated and tortuous retinal veins, with intraretinal haemorrhages all over the posterior pole with Macular Oedema (MO) (Fig 1). Fundus evaluation of the right eye demonstrated a normal optic disc with a cup to disc ratio of 0.4 and flat macula and no evidence diabetic retinopathy.

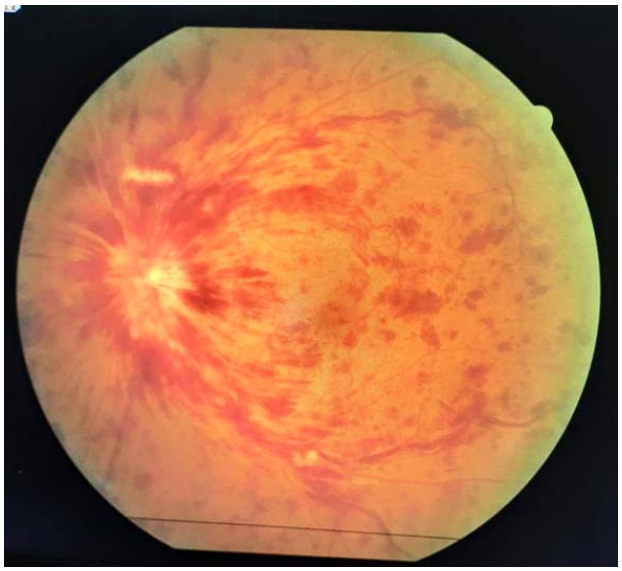


Fig 1 — Fundus Photograph

Optical Coherence Tomography (OCT) showed spongy Macular Oedema with loss of foveal contour (Fig 2).

Patient was diagnosed with unilateral non ischemic central retinal vein occlusion in the left eye.

Laboratory tests including complete hypercoagulability and thrombotic workup was done (Tables 1 & 2).

As the patient had Macular Oedema (MO), she was

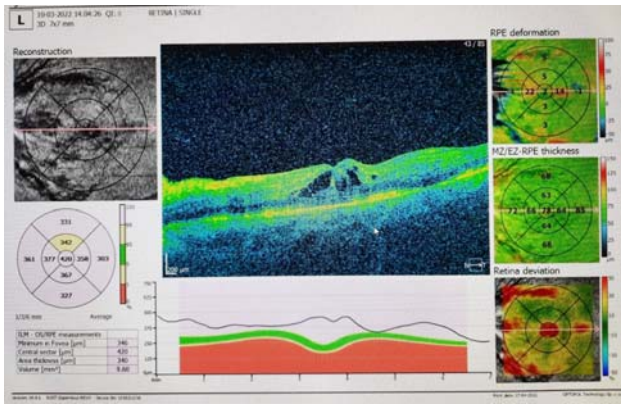


Fig 2 — Optical Coherence Tomography

Table 1

CBC with ESR	Hb 12.2 TC 8000 Platelet 1.9lakhs HCT 40 ESR 8
HbA1C	6.9
PTINR	Normal INR 0.9
APTT	Normal
S Cr	0.8mg/dl
CRP	6 (Normal)
SARS CoV IgG antibody	Positive
IgM antibody	Negative
D-dimer	690ng/ml (Normal <500)
Fasting lipid profile	Normal
ANA	Negative
Rheumatoid factor	Negative
VDRL	Negative
FTA-ABS	Negative
HIV	Negative
Serum protein electrophoresis	Normal
Haemoglobin electrophoresis	Normal

Table 2

Serum homocysteine	Normal
Folate level	Normal
B12 level	Normal
Antiphospholipid antibody titre	Not raised
Anticardiolipin antibody	Negative
Lupus anticoagulant	Negative
Functional protein C assay	Normal
Functional protein S assay	Normal
Functional antithrombin III assay	Normal
Factor V Leiden PCR assay	Negative

initiated on intra vitreal anti-VEGF (Vascular Endothelial Growth Factor) injection (Ranibizumab) with a plan to give 3 monthly doses watching for improvement in Macular Oedema and visual acuity.

The patient was started on dual antiplatelets (aspirin 75+clopidogrel 75), her anti diabetic medications were continued with good glycaemic control and she was advised close follow up for the next 6 months to check for neo-vascularisation.

Discussion and Conclusions

Young patients in the age group of 40-49 years, have an approximate global prevalence of 0.44% for Retinal Vein Occlusion (RVO)[7]. In most cases, the causative factors for RVO among the younger population is still not clear. A cohort study of 69 young CRVO patients with age <50 showed hypertension (44%), dyslipidaemia (38%) and diabetes (23%) to be the common comorbidities[8]. Though unproven, a role for dehydration in some cases has been suggested[9].

A high proportion of patients in this age group have a benign course, with spontaneous regression being more likely. Young patients with CRVO tend to have a lesser requirement for intravitreal anti Vascular Endothelial Growth Factor (VEGF) for Macular Oedema[10]. Nevertheless, poor visual outcome with severe neovascular complications can occur in around 20% of patients[6]. RVO Consultation Document, 2021 states that, if there is no evidence of neo-vascularisation or Macular

Oedema and if visual acuity is above 6/12, the patient may be observed for spontaneous regression as per the discretion of the treating Consultant.

In accordance with European Society of Retina (EURETINA) guidelines, anti VEGF are the agents of choice for the treatment of MO due to CRVO. Ranibizumab, a pan VEGF-A humanised recombinant monoclonal antibody fragment is approved by European Medicines Agency (EMA) and recommended by National institute for Health and Care Excellence (NICE) for the treatment of RVO with secondary macular oedema.

For Non-ischemic CRVO, for the first 6 months, follow up every 3 months is approved in eyes not requiring treatment. As per RVO Consultation Document 2021, Ophthalmology follow up is advised for at least 18 months even if no intervention is required from the last intravitreal therapy.

Here the diabetes was well controlled, and the coagulation work up was unremarkable except for a slightly raised D dimer which could represent an increased tendency to blood clots Post COVID. This case illustrates a scenario of unilateral CRVO where diabetes and Post COVID state are thought to be the major risk factors. Close follow up was advised to look for signs and to investigate for any neo-vascularisation.

Declarations : Institutional Ethics Committee approval was obtained for the Case Report and informed consent of the patient was obtained. There is no external funding and no competing interest.

Acknowledgement : I hereby acknowledge the contribution of Dr Manjusha Rajesh, who is a Consultant Ophthalmologist at Sreekanth Eye Care, Calicut, towards the case report who provided the fundus photo and OCT of the patient and was involved in the Ophthalmic management of the patient.

References

1 Wang, Yun BSa, Wu, Shanjun BSa; Wen, Feng MMa; Cao, Qixin BSb — Diabetes mellitus as a risk factor for retinal vein occlusion, Medicine 2020. February - Volume 99 - Issue 9 - p e19319, doi: 10.1097/MD.0000000000019319.

2 Prisco D, Marcucci R — Retinal vein thrombosis: risk factors, pathogenesis, and therapeutic approach. *Pathophysiol Haemost Thromb* 2002; **32:** 308. doi: 10.1159/000073587. [PubMed] [Google Scholar].

3 Venkatesh P — Seeking clarity on retinal findings in patients COVID-19. Lancet 2020; **396(10254):** e36. https://doi.org/10.1016/S0140-6736(20)31922-X.

4 Walinjkar JA, Makhija SC, Sharma HR, Morekar SR, Natarajan S — Central retinal vein occlusion with COVID-19 infection as the presumptive etiology. *Indian Journal of Ophthalmology* 2020; **68(11):** 2572-4, doi: 10.4103/ijo.IJO_2575_20.

5 Liu Qingyun MD, Lahey J Michael, Karlen Rachel BS, Stewart Jay M — Laboratory evaluation of hypercoagulable states in patients with central retinal vein occlusion, who are less than 56 years of age, *Retina* 2018; **3896:** 1175-9. doi: 10.1097/IAE.0000000000001661.

6 Fong ACO, Schatz H — Central retinal vein occlusion in young adults. *Surv Ophthalmol* 1993; **37(6):** 393-417. https://doi.org/10.1016/0039-6257(93)90138-W.

7 Song P, Xu Y, Zha M, Zhang Y, Rudan I — Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health* 2019; **9(1):** 010427. doi:10.7189/jogh.09.010427.

8 Koh Y-Y, Lai C-C, Wu W-C — Baseline clinical features predict visual outcome in young patients with central retinal vein occlusion. *Graefes Arch Klin Exp Ophthalmol* 2020; **258(7):** 1367-77. doi:10.1007/s00417-020-04679-8.

9 Moisseiev E, Sagiv O, Lazar M — Intense exercise causing central retinal vein occlusion in a young patient: case report and review of the literature. *Case Rep Ophthalmol* 2014; **5(1):** 116-20. doi:10.1159/000360904.

10 Rothman AL, Thomas AS, Khan K, Fekrat S — Central retinal vein occlusion in young individuals: A Comparison of Risk Factors and Clinical Outcomes. *Retina Phila Pa* 2019; **39(10):** 1917-24. doi:10.1097/IAE.0000000000002278.

Case Report

A Case of Cosmetic Poisoning : Minoxidil

Jayanta Datta[1], Dip Kumar Chowdhury[2], Atasi Roy[3]

Minoxidil is a directly acting anti-hypertensive vasodilator. It is rarely used for refractory hypertension and primarily in pattern hair loss. It is available in the market as a tablet or topical application[1].

Minoxidilis generally reserved for severely hypertensive patients not responding to at least two agents and a diuretic. Minoxidil is generally administered with a loop diuretic to prevent sodium and potassium retention. It may also cause reflex tachycardia and most of the time,it is advised with a beta blocker[2].

Minoxidil is applied topically, is generally utilized for the remedy of hair loss. It is an effective agent to promote hair growth in general population with androgenic alopecia, regardless of sex. Minoxidil must be used indefinitely to support existing hair follicles and maintain any experienced hair regrowth. Low-dose oral Minoxidil is used off-label against hair loss. Its effect in people with alopecia areata is unclear. However, the association of oral minoxidil with Janus Kinase inhibitors (JAK inhibitors), termed oral adjuvant Minoxidil, increases hair regrowth in patients refractory to JAK inhibitor monotherapy. Minoxidil is an orally used vasodilator with hair growth stimulatory antihypertensive property[3,4].

Minoxidil is converted into active metabolite Minoxidil sulfate by Sulphotransferase Enzymes. Minoxidil sulfate exerts its antihypertensive effect by opening plasma membrane Adenosine Triphosphate (ATP)-sensitive potassium channels (KATP channels), directly and rapidly relaxing the arteriolar smooth muscle and subsequent reduction of raised Systolic and Diastolic Blood Pressure through decreasing peripheral vascular resistance[5,6].

[*J Indian Med Assoc* 2023; **121(10):** 62-3]

Key words **: Vasodilator, Minoxidil.**

Case Report

A 18-year-old male with no co-morbidities presented with giddiness and vomiting after accidentally consuming 40 ml of 5% topical solution (Fig 1) of minoxidil 8 hours ago. He was conscious,oriented, afebrile, tachycardic (112/min), hypotensive (90/60 mm Hg) and Tachypneic (28/min). Initial ABG with room air revealed pH=7.32, pO2=61, pCO2=22, bicarb=18, lactate=2.6. He was started on iso-osmolar crystalloid IV fluid 1 litre bolus followed by 500 ml/h (USG guided IVC collapsibility was monitored regularly), despite which he remained Hypotensive(80/60 mm Hg), hypoxic (SpO2=89% room air)and oliguric (20 ml urine passed since admission). His Chest X-ray (Fig 2) revealed features of cardiac failure. He developed drowsiness, and auscultation revealed bilateral crackles. He was started on Oxygen Therapy and Dopamine Infusion (IVC was found to be dilated and poorly respiratory variable). He was intubated and given hypoxia. Noradrenaline and Vasopressin were added because of hypotension. Continuous arterial BP was monitored, and inotropic supports were moderated over the next 48 hours. Repeat ABG was improved as pH=7.52, pO2=120, pCO2=18, bicarb=19, lactate=1.8. Initial laboratory investigations revealed Hb=10.8 gm%, total WBC=12800/cu mm (82% neutrophils), CRP=76 mg/dl, Cr=1.8 mg/dl, Na=122 mmol/L, K=5.3 mmol/L, Trop I=negative, NT Pro BNP=7890 pg/ml, LFT=within normal limit with no coagulopathy. Echocardiography revealed no RWMA with LVEF 49%. Broad spectrum parenteral antibiotic was started. Vasopressin and dopamine were tapered off & Dobutamine infusion was introduced. Gradually, his BP was stabilized and his sensorium was improved. Urine output became normal and the lungs were clear. He was weaned off mechanical ventilation after 72 hours, and the vasopressor support was tapered off.

Editor's Comment :

- Minoxidil is an antihypertensive vasodilator, rarely used for refractory hypertension and primarily in pattern hair loss.Accidental oral ingestion of topical preparation is very rare.
- Patient with Minoxidil poisoning can present with refractory shock followed by volume overload manifested by pulmonary oedema and often is life-threatening.
- Timely use of IV fluid, inotropic agents and supportive therapy can save life.

Discussion

Minoxidil is a direct arterial vasodilator and is available as an over-the-counter drug for the topical treatment of androgenic alopecia. Our patient presented with refractory shock. The patient developed pulmonary edema and respiratory failure, which required crystalloids, triple vasopressor support and mechanical ventilation[7,8].

Department of Internal Medicine, Charnock Hospital, Kolkata 700157
[1]MD, Consultant & Head and Corresponding Author
[2]MRCPCH, Senior Registrar
[3]MD, Resident, Department of Emergency Medicine

Received on : 04/02/2023
Accepted on : 24/02/2023

Conclusion

Ingestion of topical Minoxidil can be life-threatening—emergency with refractory shock due to its vasodilatory effect. Tachycardia and fluid retentive effects can further complicate its course and management. With increased over-the-counter availability and usage of topical Minoxidil, physicians must be aware of this entity and its management[9].

Fig 1 — Consumed Minoxidil Preparation

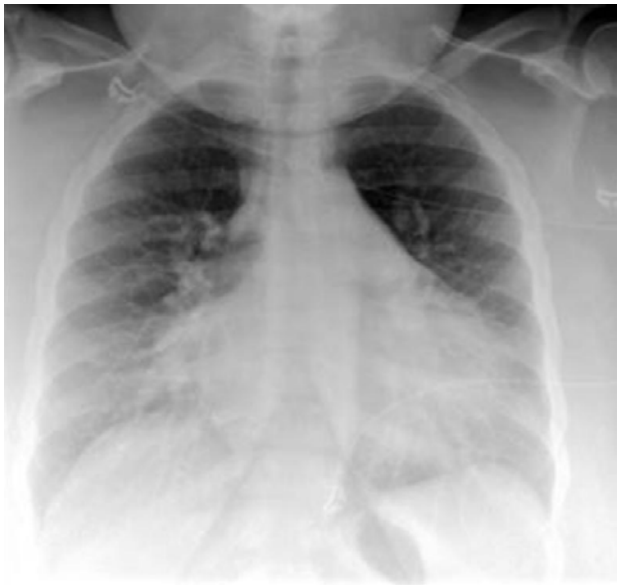


Fig 2 — X-ray shows cardiomegaly with pulmonary venous congestion

References

1 Sica DA — Minoxidil: an underused vasodilator for resistant or severe hypertension. *J Clin Hypertens (Greenwich)* 2004; **6(5):** 283-7.

2 Pettinger WA — Minoxidil and the treatment of severe hypertension. *N Engl J Med* 1980; **303:** 902-6.

3 Novak E, Frenz TZ, Headington JT — Topically applied minoxidil in baldness. *Int J Dermatol.* 1985; **24:** 82-7.

4 Spindler JR — The safety of topical minoxidil solution in the treatment of male pattern baldness; the results of a 27-center trial. *Clin Dermatol* 1998; **6:** 200-12.

5 Nielson Kudsek JE, Boesgaard S — Potassium channel opening; a new drug principle in cardiovascular medicine. *Heart* 1996; **79:** 109-16.

6 Rose SR, Tomaszewski C — Evaluation of oral and topical minoxidil exposures reported to US Poison Centres from 1985–1991. *Drug Investig* 1994; **8(2):** 81-94.

7 Allon M, hall WD, Macon EJ — Prolonged hypotension after initial minoxidil dose. *Arch Intern Med* 1986; **146:** 2075-6.

8 Shenoy S, Ganesh A, Rishi A — Dopamine versus norepinephrine in septic shock: a meta-analysis. *Crit Care* 2011; **15(suppl 1):** P89.

9 McCormick MA, Forman MH, Manoquerra AS — Severe toxicity from ingestion of a topical minixidil preparation. *Am J Emerg Med* 1989; **4:** 418-21.

Case Report

Effectiveness of Intravitreal Ranibizumab in a Postmenopausal Hypertensive Women with BROV

Vinitha Dharmalingam[1], Nirmal Fredrick[2], Sunitha Nirmal[3]

Women after menopause undergo extensive physiological changes. Hypertension is one among them which is associated with various disorders like cardiovascular disorder, renal failure, vascular occlusion in eyes, etc, we have encountered a post-menopausal woman in her early 50's with branch retinal vein occlusion and macular edema who was later diagnosed with systemic hypertension. She was started on anti-hypertensive drugs and administered intravitreal ranibizumab at the earliest. Significant reduction in macular edema was observed after two injection of ranibizumab.

[*J Indian Med Assoc* 2023; **121(10):** 64-6]

Key words **: Retinal Vein Occlusion In Postmenopausal Women, Intravitreal Ranibizumab, Branch Retinal Vein Occlusion.**

The major risk factor for Branched Retinal Vein Occlusion (BRVO) is Hypertension. Chronic increase in systemic blood pressure causes thickening of the retinal arterioles. Retinal arterioles and veins share a common adventitia at arteriovenous crossings, which causes obstruction of retinal veins leading to occlusions. Post-menopausal women with decreased oestrogen level are more prone for vascular occlusion and Macular Oedema (MO). Excellent visual outcome may be expected from patients treated with Intravitreal Ranibizumab at the earliest with proper control of Systemic Hypertension.

Case Report

53-year-old Post-menopausal women from Kanchipuram was referred to our hospital for fundus evaluation. Ocular history included complaints of sudden painless loss of vision in right eye on waking up in the morning and occasional floaters. She had no symptoms in the left eye. Patient also gave history of occasional giddiness and headache for the past 6 months. Best corrected visual acuity was 6/60 in right eye and 6/6 in left eye. IOP was found to be normal.On examination anterior segment was normal and fundus examination revealed right eye superotemporal BRVO with macular edema. Patient was subjected to fundus photograph and OCT macula. OCT showed RE macular edema with a thickness of 463 microns (Figs 1&2). Blood pressure was examined and was found to be 190/100mmHg. Other routine blood investigations were normal. Patient was started on anti-hypertensives as advised by general physician.

Department of Ophthalmology, Nirmals Eye Hospital, Chennai, Tamil Nadu 600045
[1]MBBS, Junior Consultant and Corresponding Author
[2]MBBS, DO, DNB, Managing Director
[3]MBBS, MS, Consultant Ophthalmologist

Received on : 16/08/2022
Accepted on : 21/01/2023

Editor's Comment :

- Early intervention, individualised treatment plan and regular follow up is the key to prevent vision loss in any retinal vessel occlusion.

Under aseptic precaution RE Intravitreal Ranibizumab was given 2 days after the diagnosis. Patient was started on topic antibiotic steroid eye drops and lubricants. Eye was quiet and IOP was normal on first Post-operative day.

Repeat OCT was taken 31 days after the first injection which showed minimal macula edema with thickness of 270 microns. There was gross reduction of macular edema after first Intravitreal Ranibizumab. Patient had second dose of intravitreal ranibizumab after 1 month. During the last visit OCT macula revealed no macular edema with thickness of 267 microns (Figs 3&4). Patients was advised on strict control of systemic blood pressure and regular follow up.

Discussion

Retinal Vein Occlusion (RVO) is the major vision threatening retinal vascular disease. Higher incidence of Branch Retinal Vein Occlusion (BRVO) was reported than Central Retinal Vein Occlusion (CRVO). The risk factors of RVO are closely related to cardiovascular disorders such as hypertension, dyslipidemia, smoking and diabetes mellitus[1]. Women undergo significant physiological changes during menopause including drop in estrogen level in blood. Oestrogen has vasodilator effect through endothelium-independent inhibition of vascular smooth muscle contraction and causes vasodilatation of the blood vessels. Oestradiol is used to synthesis endogenous vasodilators and decreases vascular resistance. This explains the higher incidence of systemic hypertension in Post-menopausal women. Also, incidence of RVO was found to be more in Post-

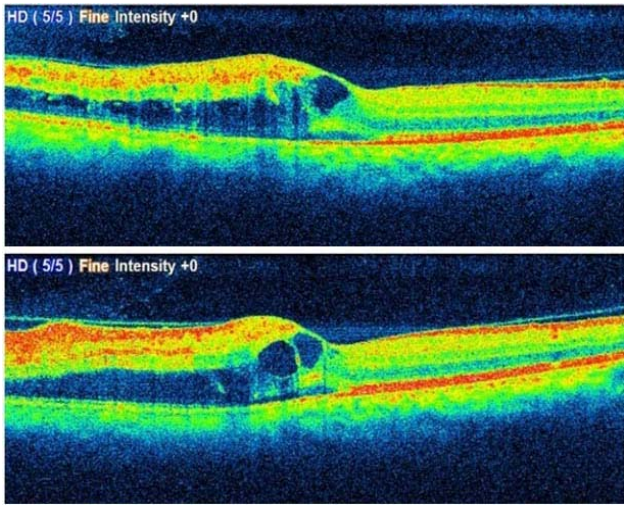


Fig 1 — Pre-OCT Image at Presentation

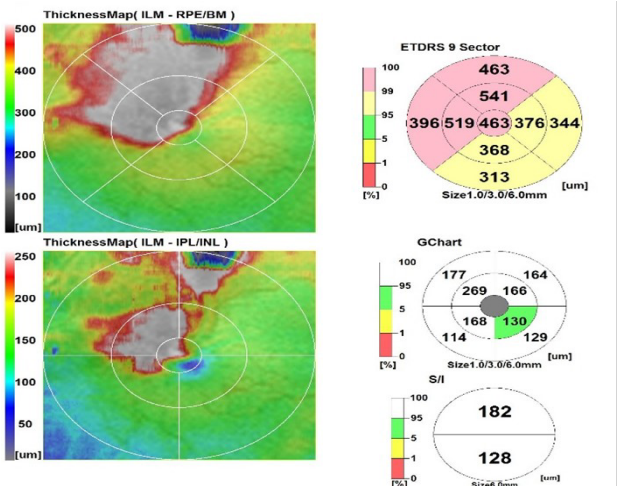


Fig 2 — Pre-OCT Map at Presentation

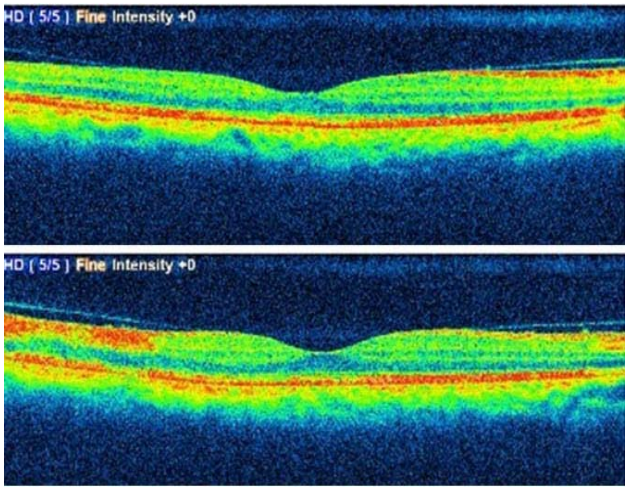


Fig 3 — Post OCT Image after Two Injections of Intravitreal Ranibizumab

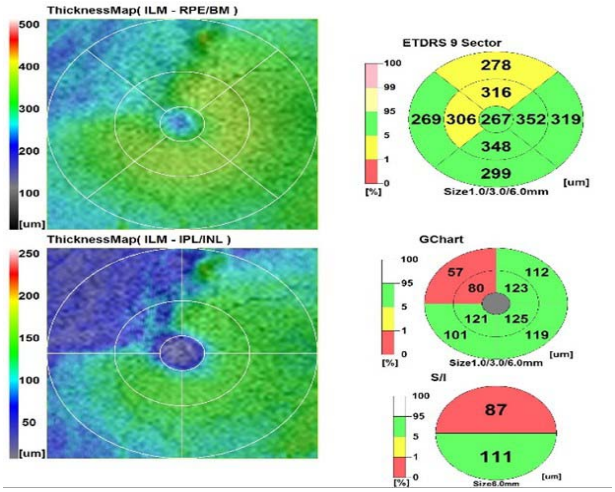


Fig 4 — Post OCT Map after Two Injections of Intravitreal Ranibizumab

menopausal women than Pre-menopausal women. Early menopause was also found to have significant association with RVO[2].

BRAVO and CRUISE studies reported greater vision improvement in patients with BRVO treated with intravitreal monthly ranibizumab for 6 months even when the patient presented with extended vision loss. Patients treated within 3 months after the onset showed better improvement in visual acuity. Extended studies of CRUISE, RETAINE and HORIZON shows that frequent follow up required because the vision did not retain in all the patients after 2 years[3].

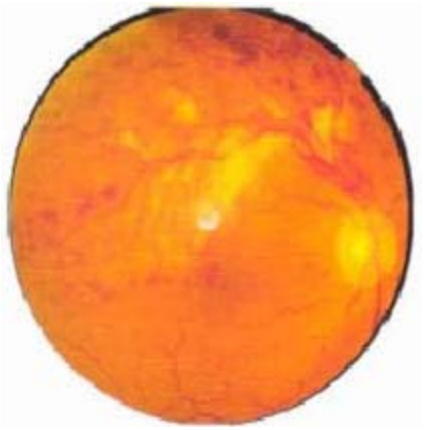


Fig 5 — Pre-fundus Image at Presentation

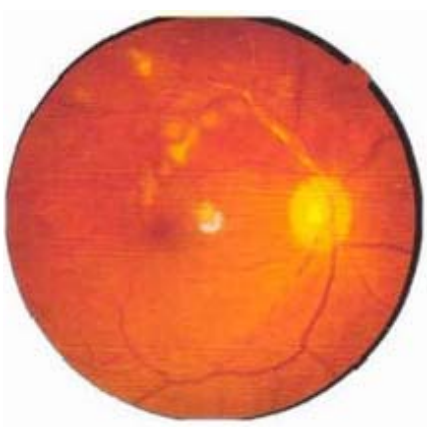


Fig 6 — Post-fundus Image after Two Injections of Intravitreal Ranibizumab

Retain study stated that there was excellent result with ranibizumab for long term outcome in patients with BRVO. Half of the patients from their study group required occasional injections after 4 years to maintain visual recovery[4]. HORIZON study suggested individualized course of ranibizumab injection and follow-up required based on the vision. Patients with CRVO may require more frequent follow-up[5].

The need for focal laser along with anti-VEGF treatment for macular oedema is still debatable. But few studies have stated that focal laser did not decrease the number of injections required or improve visual acuity in macular oedema due to BRVO. Also, Focal laser does not appear to be of additional benefit with anti-VEGF[6-8].

Intravitreal Ranibizumab injection in patients with BRVO related macular oedema as early as possible and patient individualized treatment with regular follow up is require for good vision recovery[9].

References

1 Oh Tae Ryom, Han Kyung, Choi Hong Sang, Kim Chang Seong, Bae Eun Hui, Ma Seong Kwon, *et al* — Hypertension as a risk factor for retinal vein occlusion in menopausal women - A nationwide Korean population-based study. Editor(s): Moorthy., Balaji Thas. *Medicine* 2021; **100(43):** p e27628, October 29, 2021. | DOI: 10.1097/MD.0000000000027628

2 Sungsoon Hwang, Se Woong Kang, Kyung Jun Choi, Ki Young Son, Dong Hui Lim, Dong Wook Shin, *et al* — Early menopause is associated with increased risk of retinal vascular occlusions: a nationwide cohort study. *Sci Rep* 2022; **12(1):** 6068. DOI: 10.1038/s41598-022-10088-0

3 Ashraf M, Souka AAR, Singh RP — Central retinal vein occlusion: modifying current treatment protocols. *Eye (Lond)* 2016; **30(4):** 505-14. doi: 10.1038/eye.2016.10. Epub 2016 Feb 12. DOI: 10.1038/eye.2016.10

4 Peter A Campochiaro, Raafay Sophie, Joel Pearlman, David M Brown, David S Boyer, Jeffrey S Heier, *et al* — Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. *Ophthalmology* 2014; **121(1):** 209-19. doi: 10.1016/j.ophtha.2013.08.038. Epub 2013 Oct 7.

5 Jeffrey S Heier, Peter A Campochiaro, Linda Yau, Zhengrong Li, Namrata Saroj, Roman G Rubio, *et al* — Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Randomized Controlled Trial Ophthalmology 2012; **119(4):** 802-9. doi: 10.1016/j.ophtha.2011.12.005. Epub 2012 Feb 1.

6 Peter A Campochiaro, Gulnar Hafiz, Syed Mahmood Shah, Quan Dong Nguyen, Howard Ying, Diana V Do, *et al* — Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. *Mol Ther* 2008; **16(4):** 791-9. doi: 10.1038/mt.2008.10. Epub 2008 Feb 5.

7 Meredith E Thomley, Cole N Gross, Ana Preda-Naumescu, Kelly S Chen, Thomas Swain, John O Mason Iii, *et al* — Real-World Outcomes in Patients with Branch Retinal Vein Occlusion- (BRVO-) Related Macular Edema Treated with Anti-VEGF Injections Alone versus Anti-VEGF Injections Combined with Focal Laser. *J Ophthalmol* 2021; 6641008. doi: 10.1155/2021/6641008. eCollection 2021.

8 Xiao-Xiao Feng, Cheng Li, Wan-Wen Shao, Yong-Guang Yuan, Xiao-Bing Qian, Qi-Shan Zheng, *et al* — Intravitreal anti-VEGF agents, oral glucocorticoids, and laser photocoagulation combination therapy for macular edema secondary to retinal vein occlusion: preliminary report. *Int J Ophthalmol* 2018; **11(3):** 429-37. Published online 2018 Mar 18. doi: 10.18240/ijo.2018.03.13

9 Rezar S, Eibenberger K, Bühl W, Georgopoulos M, Ursula Schmidt-Erfurth, Stefan Sacu, *et al* — Anti-VEGF treatment in branch retinal vein occlusion: a real-world experience over 4 years. *Acta Ophthalmol* 2015; **93(8):** 719-25. doi: 10.1111/aos.12772. Epub 2015 Jun 24.

Drug Corner

Omega-3 Fatty Acids Combined with Statins in Atherogenic Dyslipidemia : A Comprehensive Review

Sanjay Kalra[1], Anish Desai[2]

Omega-3 fatty acids, an integral component of cardiovascular health, have garnered significant attention in the context of atherogenic dyslipidemia, a condition closely linked to cardiovascular disease (CVD) and characterized by elevated triglyceride levels, reduced high-density lipoprotein cholesterol (HDL-C), and an abundance of small dense LDL particles (sdLDL). This distinctive lipid profile is intricately associated with insulin resistance, obesity, and metabolic syndrome, collectively amplifying the risk of atherosclerotic CVD. Notably, Indian populations often exhibit this particular pattern of atherogenic dyslipidemia.

While statins have long been the cornerstone of dyslipidemia management, primarily focusing on lowering LDL-C levels and reducing CVD risk, the unique lipid profile observed in Indian individuals necessitates a more comprehensive approach. This comprehensive review explores the current knowledge regarding combining omega-3 fatty acids and statins as a potential approach to address the triad of atherogenic dyslipidemia and reduce the residual CV risk.

[*J Indian Med Assoc* 2023; **121(10):** 67-71]

Key words **: Omega 3 fatty acids, Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA), Atherogenic Dyslipidemia.**

Atherogenic Dyslipidemia :

Atherogenic Dyslipidemia represents a cluster of lipid abnormalities that collectively contribute to a heightened risk of CVD. The typical features of atherogenic dyslipidemia include elevated triglycerides, increased levels of small dense LDL particles, and decreased levels of HDL-C[1].

In recent years, the Indian population showed an increasing incidence of AD and CVD compared to the western population, possibly due to adverse lifestyle changes such as physical inactivity, diet deficient in PUFA and a higher genetic predisposition[1]. According to the ICMR-INDIAB study, which included 2042 subjects for lipid evaluation, dyslipidemia is highly prevalent among Indian adults, with 18% of the study participants having atherogenic dyslipidemia, characterized by elevated TG levels and high HDL-C levels[2]. The prevalence of atherogenic sdLDL was significantly higher in Asian Indians than in Whites in the USA (44% *versus* 21%; $p < 0.05$)[3].

Pathophysiology[1,4,5]

Elevated Triglyceride-rich Lipoprotein (TRL) and small-dense Low-density Lipoprotein (sdLDL) particles are hallmarks of atherogenic dyslipidemia, and their cholesterol content is hypothesized to drive atherosclerotic risk. Hypertriglyceridemia is characterized by increased generation and/or decreased catabolism of VLDL particles. It is also associated with enhanced Cholesterol-ester Transfer Protein (CETP) activity. CETP mediates the exchange of triglycerides and cholesterol esters between Triglyceride-rich Lipoproteins (TRL) and LDL particles in hypertriglyceridemia. At the same time, TG-enriched LDLs are good substrates of Hepatic Lipase (HL), which further converts them into smaller and denser forms, ie, sdLDL. The result is increased cholesterol-enriched TRL particles and sdLDL particles of varying triglyceride and cholesterol content. TRL and sdLDL cholesterol content is associated with an increased risk of cardiovascular disease outcomes of varying magnitude across vascular territories (Fig 1). Low HDL-C levels in atherogenic dyslipidemia result in impaired reverse cholesterol transport, reducing the protective capacity of HDL particles against atherosclerosis.

Statins : Mainstay therapy for dyslipidaemia management[6,7]

Statins, a class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, have revolutionized the management of dyslipidemia. They are highly effective at reducing LDL-C levels and are associated with substantially reducing cardiovascular events and mortality. Multiple primary and secondary prevention trials have shown a

[1]MBBS, MD (Medicine), DM (Endocrinology), Department of Endocrinology, Bharti Hospital, Karnal 132001, Haryana

[2]MD, FCP, PGDHEP, Clinical Pharmacologist & Nutraceutical, Physician, Founder & CEO, IntelliMed Healthcare Solutions, Kurla, Mumbai 400070

Received on : 03/10/2023
Accepted on : 04/10/2023

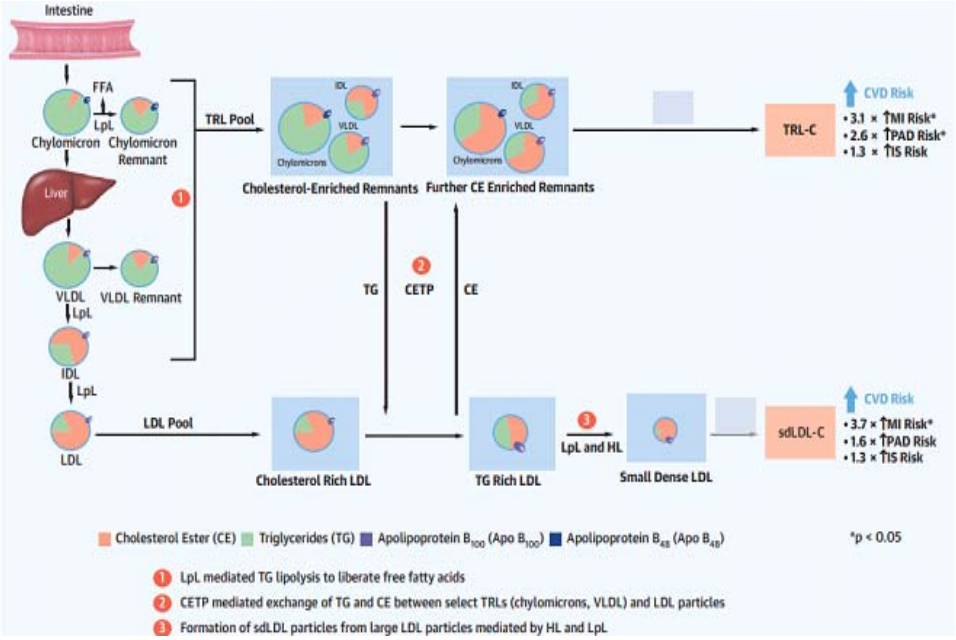


Fig 1 — Pathophysiology of atherogenic dyslipidemia[5]

Apo = apolipoprotein; CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; FFA = free fatty acids; HL = hepatic lipase; IDL = intermediate-density lipoprotein; IS = ischemic stroke; LDL = low-density lipoprotein; LpL = lipoprotein lipase; MI = myocardial infarction; PAD = peripheral artery disease; TG = triglycerides; VLDL = very-low-density lipoprotein

significant reduction of 25% to 35% in the risk of cardiovascular events with statin therapy.

Limitations of statin monotherapy

- Residual CVD Risk with statins- Epidemiological studies have shown that, in addition to elevated LDL-C levels, both elevated baseline levels of TGs and low levels of HDL-C are independent predictors of the risk of CHD. However, residual risk persists even among patients treated with high-intensity statins, particularly in high-risk subjects with pre-existing ASCVD, T2DM, or metabolic syndrome. Patients with known ASCVD on statin therapy estimated the mean 5-year ASCVD recurrent event risk of 21.1%, with 16% of patients experiencing a recurrent event over the 4.2-year follow-up[8,9].
- On the other hand, contemporary clinical and genetic evidence suggests that TG, especially TRLs and apoprotein C3, play essential roles in the etiology of atherosclerosis. Therefore, TG and TRLs are becoming therapeutic targets for lowering the risk of ASCVD[4] . Statins have a limited impact on triglycerides and HDL-C levels, leaving individuals with atherogenic dyslipidemia at persistent cardiovascular risk[8,10].

Hence, Indian patients with dyslipidemia require attention to all aspects of atherogenic dyslipidemia in addition to the focus on LDL-C lowering[1,3,4].

Omega-3 Fatty Acids : A Potential Adjunctive Therapy to statins in management of atherogenic dyslipidemia

Introduction

Omega-3 fatty acids (O3FA), particularly Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), have garnered significant attention for their potential triglyceride-lowering effect. In addition, they seem to exhibit pleiotropic effects in reducing plaque instability and pro-inflammatory mediators that underlie and potentiate atherogenesis. These polyunsaturated fatty acids are abundant in fatty fish and are available as fish oil supplements. Omega-3 fatty acids have multifaceted effects, making them an attractive option as an adjunct to statin therapy to provide an enhanced reduction of the triglyceride/total cholesterol/high-density lipoprotein cholesterol in comparison to statin alone and thus helps in addressing the triad of atherogenic dyslipidemia and reducing CVD risk[11].

Mechanisms of Action

The potential benefits of O3FA in atherogenic dyslipidemia are rooted in their multifaceted mechanisms of action (Table 1).

These mechanisms complement the primary action of statins, which primarily target LDL-C reduction and offer CV protection. Combining statins and Omega-3 fatty acids may thus offer a more comprehensive approach to managing atherogenic dyslipidemia and reducing residual CV risk[11-14].

Importance of prescription omega 3 fatty acids product over non-prescription fish oil supplements

Prescribed O3FAs supplements have been shown to reduce fasting and non-fasting TG levels by 20%-50% and increase the LDL particle size[5,15]. Nonprescription fish oil products are not interchangeable with prescription Omega-3 products due to differences in O3FA content and bioavailability. Prescription O3FA supplements have undergone more rigorous safety and efficacy evaluation than dietary supplements (Table 2)[15,16].

Clinical Trials for prescription Omega-3 fatty acids as an adjunctive therapy to statins

Clinical trials examining omega-3 fatty acids as adjunctive therapy to statins have shown potential benefits in improving the triad of atherogenic dyslipidemia in patients with persistent hypertriglyceridemia despite statin therapy. Recently, REDUCE-IT trialdemonstrated a significant reduction in cardiovascular events when high-dose EPA was added to statin therapy in patients with elevated triglycerides and established cardiovascular disease.

Table 1 — *Mechanism of action of omega-3 fatty acids*[12-14]

Effect of O3FA	Mechanism
Triglyceride reduction - A hallmark of atherogenic dyslipidemia	1. Increases the β-oxidation of fatty acids by activating peroxisome PPAR-a, thus reduces the substrate required for TG and VLDL synthesis. 2. Decreases hepatic lipogenesis by suppressing the expression of sterol regulatory element-binding protein-1c. This, in turn, leads to reduced expression of cholesterol-, fatty acid-, and TG-synthesizing enzymes. 3. Inhibit key enzymes involved in hepatic TG synthesis, such as phosphatidic acid phosphatase and diacylglycerol acyltransferase. 4. Increase the expression of Lipoprotein Lipase (LPL), a key component of the triglyceride-rich lipoprotein (TRL) biosynthetic pathways, leading to increased TG removal from circulating VLDL and chylomicron particles. 5. Reduces Remanent lipoprotein (RLP).
Anti-Inflammatory	Have anti-inflammatory properties that may help reduce inflammation within the arterial walls, thus contributing to prevention of plaque development and plaque stability.
Improved Endothelial Function	Can enhance endothelial function, promoting healthy blood vessel dilation and reducing the risk of endothelial dysfunction, a critical early step in atherosclerosis.
Potential Plaque Stabilization	O3FA may stabilize atherosclerotic plaques, reducing the likelihood of plaque rupture and thrombosis.

These trials are motivated by the idea that omega-3 fatty acids, particularly EPA and DHA, offer complementary benefits to statins. While statins primarily target LDL cholesterol, omega-3 fatty acids provide anti-inflammatory, triglyceride-lowering, and potential anti-atherosclerotic effects.Numerous Randomized Controlled Trials (RCTs) and observational studies have investigated the use of Omega-3 fatty acids in combination with statins in patients with persistent hypertriglyceridemiato manage atherogenic triad in short term and reduce the CV risk in long-term,as presented in Tables 3 and 4.

Safety and Tolerability

One of the notable advantages of Omega-3 fatty acid supplementation is its generally favorable safety profile. In clinical trials, adverse effects are typically mild, including fishy burps and gastrointestinal symptoms. Serious adverse events are rare, making Omega-3s well-tolerated by most individuals.

However, there has been an ongoing debate regarding the potential bleeding risk associated with high-dose Omega-3 supplementation. This concern arises becauseO3FA can have antithrombotic effects, which may increase the risk of bleeding events. The risk of bleeding is relatively low in most cases but may warrant caution, especially in individuals at increased risk of bleeding, such as those on anticoagulant therapy[27-29].

Table 2 — *Comparison of prescription O3FA medications and nonprescription fish oil preparations*[16]

	Prescription Omega-3 products	Nonprescription Fish oil Preparation
FDA classification	Prescription drug	Dietary supplement
FDA-Approved indication to treat elevated TG	✓	–
Efficacy verified	✓	–
Consistent content	✓	Varies
Consistent purity	✓	It may contain saturated fat, oxidized fatty acids, contaminants, and/or additional calories.
Tolerability	Well-tolerated	Burping, fishy taste, dyspepsia

Conclusion

In conclusion, atherogenic dyslipidemia,a unique pattern of dyslipidemia in Indians, represents a significant risk factor for cardiovascular disease, and its management is critical for reducing CVD risk. Statins have long been the primary therapy for dyslipidemia, primarily by lowering LDL-C levels. However, individuals with atherogenic dyslipidemia often experience residual cardiovascular risk with statin monotherapy, and it also has a limited impact on triglycerides and HDL-C levels. Therefore,additional therapies for the comprehensive management of atherogenic dyslipidemia should be considered apart from LDL-C lowering.

Omega-3 fatty acids, particularly EPA and DHA, have emerged as potential adjunctive therapies to address a triad of atherogenic dyslipidemia and reduce the residual CV risk. The combination of O3FA with statins offers a multifaceted approach by targeting triglyceride reduction, anti-inflammatory effects, improved endothelial function, and potential plaque stabilization. The choice of Omega-3 formulation, dose, and patient population may all influence the clinical benefits of this combination therapy.

Table 3 — *Clinical trials demonstrating the effect of Omega 3 fatty acids on TG levels and other lipid parameters (short-term effect of O3FA)*

Study	Patient characteristics	Study design	No. of patients	Treatment Duration	Treatment groups	Results
Woo J, 2021[14]	Patients who had residual hypertriglyceridemia after a 4-week run-in period of atorvastatin treatment	Multicenter, randomized, double-blind, placebo-controlled study,	200	8 weeks	FDC atorvastatin/O3FA(40 mg/4 g) vs. Atorvastatin + placebo	In patients with residual hypertriglyceridemia despite receiving statin treatment, a combination of high-dose atorvastatin/ O3FA was associated with a **greater reduction of triglyceride and non–HDL-C** compared with atorvastatin + placebo without significant adverse events.
ROMANTIC Trial- (Kim C, 2017)[15]	Residual hypertriglyceridemia (Fasting TG level ≥200 mg/dL and <500 mg/dL) despite statin treatment	Multicenter, randomized, double-blind, placebo-controlled study.	201	8 weeks	Rosuvastatin20mg/d + O3FA 4g/d vs. Rosuvastatin 20 mg/d	In patients with residual hypertriglyceridemia despite statin treatment, a combination of O3FA and rosuvastatin produced a **greater reduction of TGs and non–HDL-C** than rosuvastatin alone.
ESPRIT Trial-Maki K, 2013[16]	Persistent hypertriglyceridemia (fasting TG levels ≥200mg/dL and 500 mg/dL and treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for cardiovascular	Double-blind, parallel-group study	627	6 weeks	4g/dOM3-FFA or 2g/dOM3-FFA (plus 2g/d OO),or OM3-FFA 4g/d vs.Capsules of control (olive oil [OO])	OM3-FFA was well tolerated and lowered non–HDL-C and TG levels at both 2-and4-g/d dosagesinpatientswithpersistenthypertriglyceridemiataking a statin.
Jun J, 2020[17]	Residual hypertriglyceridemia (fasting TG levels ≥200 and <500 mg/dL and LDL-C levels <110mg/dL)	Randomized, double-blind, placebo-controlled, parallel-group, and phase III multicenter study	200	8 weeks	OM3FAs 4 gm + atorvastatin calcium 20 mg or atorvastatin 20 mg + placebo groups	Addition of O3FAs to atorvastatin **improved TG and non-HDL-C** levels to a significant extent compared to atorvastatin alone in subjects with residual hypertriglyceridemia.
Us G, 2022[18]	Hyperlipidemic patients (non-HDL-C >130 mg/dL)receiving stable statin therapy.	Randomized, placebo-controlled, double-blind, parallel-group study	44	8 weeks	Atorvastatin + 4 g/day EPA + DHA (3000 mg EPA + 1000 mg DHA) and the placebo group receivedAtorvastatin + 4g/day olive oil	In hyperlipidemic patients on a stable statin prescription, OM3 plus atorvastatin **improved small dense LDL concentrations, non-HDL-C, VLDL-C and TG to a greater extent than atorvastatin alone**.
COMBOS STUDY (COMBination of prescription Omega-3 with Simvastatin)[19]	HTG patients (TG levels ≥200 and < 500 mg/dL)	multicenter, randomized, double-blind, placebo-controlled, parallel-group study	256	8 weeks	O3FA 4 g/d* + simvastatin 40 mg/d vs. Placebo + simvastatin	The combination of O3FA + simvastatin, as compared to monotherapy with a statin, showed a significantly greater reduction in non-HDL-C (-9.0% vs -2.2%), TG (29.5% vs 6.3%) and VLDL-C (27.5% vs 7.2%), total cholesterol: HDL-C ratio (9.6% vs 0.7%), a significant increase in HDL-C levels (3.4% vs -1.2%). There was no significant difference in the frequency of AEs between groups. Drug-related serious AEs were not found.

Table 4 — *Clinical trials demonstrating the effect of Omega 3 fatty acids on CV risk reduction (Long-term effect of O3FA)*

Study	Patient characteristics	Study design	No. of patients	Treatment Duration	Treatment groups	Results
REDUCE-IT study[20]	Patients at high risk for CV events due to elevated TG levels (135-499 mg/dL) and with established CVD or DM aged≥50 years + ≥1 risk factor for CVD, well-controlled LDL-C (40-100 mg/dL) and on statin therapy	Multicenter, randomized, double-blind, placebo-controlled trial	8179	4.9 years	2 g of EPA BID vs. placebo.	Icosapent Ethyl, as compared to placebo, demonstrated an: • **25% reduction** in risk of development of composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina **26% reduction** in risk of development of composite of CV death, non-fatal MI, or non-fatal stroke.
GISSI-P[21]	Patients who have suffered from MI within 3 months	Multicenter, open-label	11,324	3.5 years	O3FA (1 g daily) vs. vitamin E (300 mg daily) vs both or none	O3FA but not vitamin E demonstrated an • **10% reduction** in risk of developing composite of death, non-fatal myocardial infarction, and stroke. • **14% reduction** in risk of death **17% reduction** in risk of CV death.
EVAPORATE Trial- Budoff M, 2020[22]	Patients with Elevated Triglycerides (TG levels 135-499 mg/dL) on Statin Therapy	Randomized, double-blind, placebo-controlled trial	80	9 months	EPA 4mg/day	Significant slowing of progression was seen with total plaque, noncalcified plaque, fibrous, and calcific plaque volumes. Of note, total plaque was slowed by 42% (p=0.0004) and noncalcified plaque by 19% (p=0.010).
Fan H, 2021[23]	Inclusion criteria for trials: • Age ≥18 years • Diagnosis of coronary artery disease or known coronary atherosclerosis • Effect of statins + O3FA on coronary arterial plaque vs. statin therapy	Meta-analysis includes 8 RCTs	803	≥ 6 months	Statin + O3FA vs. Statin alone	O3FA combined with statins is **superior** to statin monotherapy **in stabilizing and promoting coronary plaque regression** and may help to reduce the occurrence of cardiovascular further events.

Acknowledgement

We acknowledge Mr Vikas S Singh and Dr Manish R Garg from IntelliMed Healthcare Solutions for their contribution in drafting of manuscript.

References

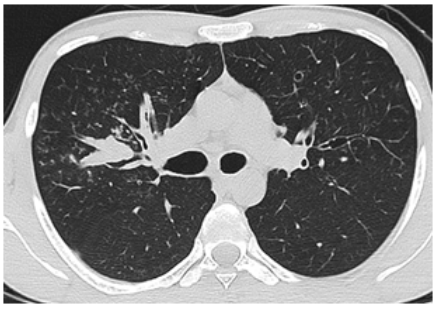
1 Manjunath CN, Rawal JR, Irani PM, Madhu K — Atherogenic dyslipidemia. *Indian journal of endocrinology and metabolism* 2013; **17(6):** 969.
2 Puri R, Mehta V, Iyengar SS, Narasingan SN, Duell PB, Sattur GB, *et al* — Lipid Association of India expert consensus statement on management of dyslipidemia in Indians 2020: part III. *The Journal of the Association of Physicians of India* 2020; **68(11 [Special]):** 8-9.
3 Puri R, Mehta V, Duell PB, Wangnoo SK, Rastogi A, Mohan V, *et al* — Management of diabetic dyslipidemia in Indians: Expert consensus statement from the Lipid Association of India. *Journal of clinical lipidology* 2023; **17(2):** e1-4.
4 Nguyen VS, Tran XT, Vo TD, Le QT — Residual Cardiovascular Risk Factors in Dyslipidemia. InRisk Factors for Cardiovascular Disease 2021 Oct 14. IntechOpen.
5 Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD — Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. *Journal of the American College of Cardiology* 2020; **75(17):** 2122-35.
6 Liao JK — Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. *The American journal of cardiology* 2005; **96(5):** 24-33.
7 Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al — Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; **2013(1):** CD004816.
8 Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE — Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *Journal of the American College of Cardiology* 2018; **72(3):** 330-43.
9 Wong ND, Zhao Y, Xiang P, Coll B, López JA — Five-year residual atherosclerotic cardiovascular disease risk prediction model for statin treated patients with known cardiovascular disease. *The American journal of cardiology* 2020; **137:** 7-11.
10 Bitzur R, Cohen H, Kamari Y, Shaish A, Harats D — Triglycerides and HDL cholesterol: stars or second leads in diabetes? *Diabetes care* 2009; **32(Suppl 2):** S373.
11 Vecka M, Dušejovská M, Stankova B, Zeman M, Vávrová L, Kodydková J, *et al* — N-3 polyunsaturated fatty acids in the treatment of atherogenic dyslipidemia. *Neuro Endocrinol Lett* 2012; **33(Suppl 2):** 87-92.
12 Kromhout D, Yasuda S, Geleijnse JM, Shimokawa H — Fish oil and omega-3 fatty acids in cardiovascular disease: do they really work? *European heart journal* 2012; **33(4):** 436-43.
13 Krupa K — Omega-3 fatty acids. Available [online] at URL: https://www.ncbi.nlm.nih.gov/books/NBK564314/. As accessed on 10th October 2023.
14 Backes J, Anzalone D, Hilleman D, Catini J — The clinical relevance of omega-3 fatty acids in the management of hypertriglyceridemia. *Lipids in Health and Disease* 2016; **15(1):** 1-2.
15 Bays HE, Tighe AP, Sadovsky R, Davidson MH — Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications. *Expert Rev Cardiovasc Ther* 2008; **6**: 391-409.
16 Virani SS — 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2021; **78**: 960-93.
17 Woo JS, Hong SJ, Cha DH, Kim KS, Kim MH, Lee JW, *et al* — Comparison of the efficacy and safety of atorvastatin 40 mg/ù-3 fatty acids 4 g fixed-dose combination and atorvastatin 40 mg monotherapy in hypertriglyceridemic patients who poorly respond to atorvastatin 40 mg monotherapy: an 8-week, multicenter, randomized, double-blind phase III study. *Clinical Therapeutics* 2021; **43(8):** 1419-30.
18 Kim CH, Han KA, Yu J, Lee SH, Jeon HK, Kim SH, *et al* — Efficacy and safety of adding omega-3 fatty acids in statin-treated patients with residual hypertriglyceridemia: ROMANTIC (Rosuvastatin-OMAcoriN residual hyperTrIgly Ceridemia), a randomized, double-blind, and placebo-controlled trial. *Clinical therapeutics* 2018; **40(1):** 83-94.
19 Maki KC, Orloff DG, Nicholls SJ, Dunbar RL, Roth EM, Curcio D, *et al* — A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). *Clinical therapeutics* 2013; **35(9):** 1400-11.
20 Jun JE, Jeong IK, Yu JM, Kim SR, Lee IK, Han KA, *et al* — Efficacy and safety of Omega-3 fatty acids in patients treated with statins for residual hypertriglyceridemia: a randomized, double-blind, placebo-controlled clinical trial. *Diabetes & Metabolism Journal* 2020; **44(1):** 78-90.
21 Dogay Us G, Mushtaq S — N-3 fatty acid supplementation mediates lipid profile, including small dense LDL, when combined with statins: a randomized double blind placebo controlled trial. *Lipids in Health and Disease* 2022; **21(1):** 1-0.
22 Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, *et al* — Combination of prescription Omega-3 with Simvastatin (COMBOS) Investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clinical therapeutics* 2007; **29(7):** 1354-67.
23 Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, *et al* — Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *New England Journal of Medicine* 2019; **380(1):** 11-22.
24 Marchioli R — Dietary supplementation with N-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. *Lancet* 1999; 354: 447-55.
25 Budoff MJ, Muhlestein JB, Bhatt DL, Le Pa VT, May HT, Shaikh K, *et al* — Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: a prospective, placebo-controlled randomized trial (EVAPORATE): interim results. *Cardiovascular research* 2021; **117(4):** 1070-7.
26 Fan H, Zhou J, Yuan Z — Meta-analysis comparing the effect of combined omega-3+ statin therapy versus statin therapy alone on coronary artery plaques. *The American Journal of Cardiology* 2021; **151:** 15-24.
27 Lovaza — USFDA PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021654s043lbl.pdf.
28 Fish oils in cardiovascular prevention: new evidence, more questions. https://cardiologie-universitaire-geneve.ch/wp-content/uploads/2022/01/Baris_Gencer_JeudI_20_01_2022_Omega3_CV_Prevention.pdf.
29 Kromhout D, Yasuda S, Geleijnse JM, Shimokawa H — Fish oil and omega-3 fatty acids in cardiovascular disease: do they really work? *Eur Heart J* 2012; **33:** 436-43.

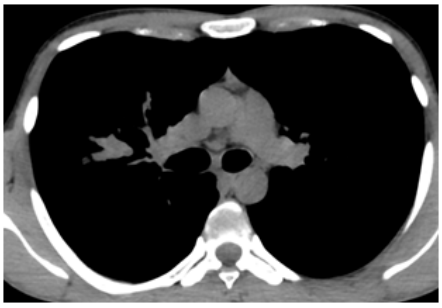
Image in Medicine

Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

A 35-year-old known Asthmatic, presented with cough with expectoration since 1 month.





Questions :

(1) What is the Diagnosis ?
(2) What is the Pathology of this condition?

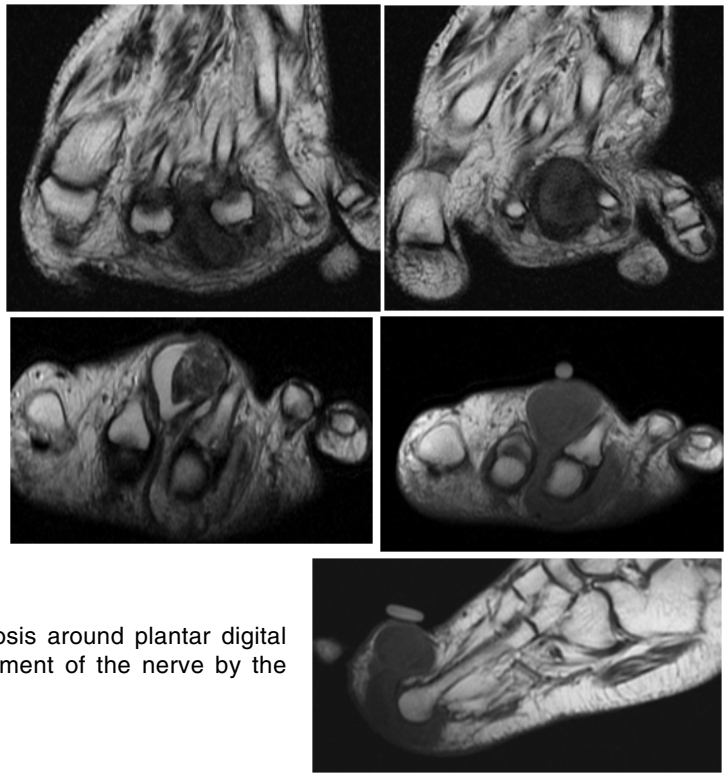
Answers :

(1) Tubular Bronchiectasis is seen in right upper lobe with endoluminal hyperdense impaction which shows V-Y branching pattern (finger in glove sign) with surrounding centrilobular nodules, these findings are suggestive of Allergic Bronchopulmonary Aspergillosis (ABPA).

(2) Allergic Bronchopulmonary Aspergillosis (ABPA) is a hypersensitivity response towards Aspergillus (fumigates) species, which grows within the lumen of bronchi without invasion. It usually affects asthmatic and atopic patients. Microscopically the dilated bronchi are filled with mucus admixed with eosinophils, fungal hyphae and charcot-leyden crystals.

Quiz 2

A 44-year-old male presented with painful gradually increasing swelling in inter-metatarsal space and dorsum of foot.



Questions :

(1) What is the Diagnosis ?
(2) What is the Pathology?

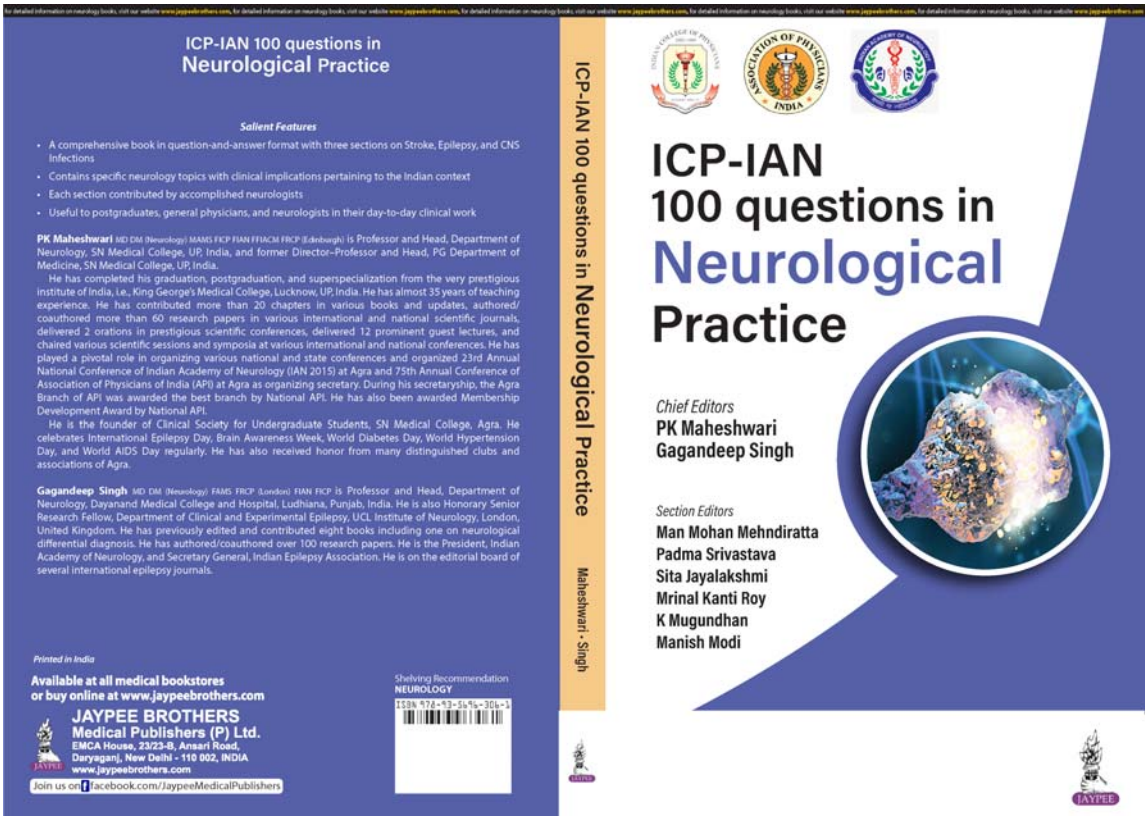
Answers :

(1) A well defined dumb-bell shaped low signal intensity lesion with surrounding fluid intensity is seen in 2nd and 3rd web spacewhich extends into plantar and dorsal aspect of foot. No erosion of adjacent bone is seen. These imaging findings are in favour of Morton neuroma with intermetatarsal bursitis.

(2) Morton neuroma is due to perineural fibrosis around plantar digital nerve. It is thought to be due to chronic entrapment of the nerve by the intermetatarsal ligament.

Department of Radiology, Picture This by Jankharia, Mumbai, Maharashtra 400004
[1]MD, DNB (Radiology)
[2]MD, DMRD (Radiology)

Book Review



Hundred Questions on Neurological Disorders, ICP-IAN 100 Questions in Neurological Practice by Gagandeep Singh PK Maheshwari

The monograph on "Hundred Questions on Neurological Disorders" is published by Jaypee Brothers Medical Publishers under the aegis of Indian College of Physicians. It has been edited Dr P K Maheswari Professor and Head of Neurology S N Medical College Agra and Dr Gagandip Singh, Professor and Head of Neurology Dayanand Medical College and Hospital Ludhiana, two eminent neurologists of the country. It is a comprehensive compilation of questions and answers on topics divided into three sections —

(a) Epilepsy - Section editors- Dr Mrinal Kanti Roy, Dr Sita Jayalakhshmi

(b) Stroke - Section Editors – Dr M M Mehndiratta , MV Padma Srivastava

(c) Infections of Nervous System – Section editors – Dr K Mugundhan, Manish Modi

Each section dwells upon issues commonly encountered by treating physicians and neurologists in their day to day practice. The monograph has a unique format – it addresses practical, real- life scenarios of clinical significance, providing the readers with readymade evidence - based answers to their queries. These will be of immense help in clinical decision making in day to day practise.

With rapid advancement in medical science, it is often difficult for a busy physician and neurologist to keep pace with modern medicine.

The book incorporates questions in three important chapters of Neurology in the Indian Context keeping in mind the significance of such an approach for the betterment of standard of care. The authors have meticulously written their answers in a lucid way for easy grasp and assimilation of the topics by the readers. This has been possible because of the vast experience, expertise and clinical acumen of the authors. The readers will find interest and enthusiasm in going through the chapters.

Not only the practitioners but the post graduate and post doctoral trainees will benefit immensely from these frequently asked questions in their examination preparation.

Hence this long awaited venture of having a monograph on selected chapters of Neurology , was conceived jointly from IAN and API-ICP forums.This monograph will act as a ready reckoner, especially when confronted with clinical conundrums encountered in daily practice and teaching.

The book is available at all medical bookstores or online at www.jaypeebrothers .com

Prof (Dr) Nandini Chatterjee
MD, FRCP (Glasgow), FICP, Professor, Department of Medicine, IPGME&R and SSKM Hospital, Kolkata 700020 and Hony Editor, JIMA

Letter to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Evaluating Contraceptive Use among Women in Gujarat, India

Sir, — India is a heavily populated country and efforts to control its population are being taken. However, it is surprising that even though most women in India know about contraception, and certain group (like young married couples) want to avoid pregnancy, the actual use of contraception is relatively low[1]. Patterns of contraceptive use are multifactorialbut the sampling frame of this study is carefully chosen to overcome the variations in the population. This study aims to evaluate contraceptive usage among women of Gujarat, India to correlate its effects on number of the kids, number of unplanned pregnancies. The correlation between contraceptive use and the level of education is explored.

Methodology :

This study has been conducted in Ahmedabad, Gujarat. The questionnaire included questions of age, education status, marital status, whether sexually active or not, contraceptive used number of kids and number of unplanned pregnancies. One-way ANOVA between contraceptives used and the number of unplanned pregnancies is shown in Tables 3 and 4 with Student Newman-Keuls Post HOC analysis. Similarly, one-way ANOVA between contraceptives used and the number of kids is shown in Tables 5 and 6 with Student Newman-Keuls Post HOC analysis. Data analysis was done using IBM SPSS.

Results :

Total 320 responses were received. In Tables 1 we see that there is a statistically significant association ($p<0.05$) between using natural methods or no contraception and a higher number of unplanned pregnancies. In Tables 2 we can see that using no contraception or natural methods of contraception is linked ($p<0.05$) to a higher number of kids as shown in the table. A significant difference can be established between those using scientifically approved contraception when compared to those who used natural methods and no contraception.

Discussion :

In India the major root cause of hesitancy has been established as the lack of awareness on correct use of contraception[2] and about the side effects that they can cause. The study further establishes the findings of many previous studies which show that level of education is positively linked to contraceptive use and negatively linked to fertility[3]. A silver lining must be that India is increasingly seeing a rise in contraceptive use by uneducated women[4], which helps progress the population control goals of the country.

Table 1 — *Number of unplanned Pregnancies*

Student-Newman-Keuls[a,b,c]		Subset	
Contraceptive Used	**N**	**1**	**2**
Pills	27	0.11	
IUD	36	0.31	
Condom	58	0.43	
Natural methods	45		0.80
None	154		0.92
Significance		0.188	0.528

Means for groups in homogeneous subsets are displayed. Based on observed means. The error term is Mean Square (Error) = 0.754.
a = Uses Harmonic Mean Sample Size = 45.138.
b = The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.
c = Alpha = 0.05.

Table 2 — *Number of Kids*

Student-Newman-Keuls[a,b,c]		Subset	
Contraceptive Used	**N**	**1**	**2**
Pills	27	1.11	
IUD	36	1.25	
Condom	58	1.29	
Natural methods	45		1.67
None	154		1.75
Significance		0.532	0.637

Means for groups in homogeneous subsets are displayed. Based on observed means. The error term is Mean Square (Error) = 0.649.
a = Uses Harmonic Mean Sample Size = 45.138.
b = The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.
c = Alpha = 0.05.

In conclusion we can say that contraceptive use is an integral part of our population control goals. We should work towards shedding a light on its benefits and its drawbacks must be acknowledged and addressed.

References

1 Darroch JE, Singh S — Trends in contraceptive need and use in developing countries in 2003, 2008, and 2012: an analysis of national surveys. *The Lancet* 2013; **381(9879):** 1756-62.
2 Mishra VK, Retherford RD, Nair PS, Feeney G — Reasons for discontinuing and not intending to use contraception in India.
3 Visaria L — Regional variations in female autonomy and fertility and contraception in India. 1993.
4 McNay K, Arokiasamy P, Cassen R — Why are uneducated women in India using contraception? A multilevel analysis. *Population Studies* 2003; **57(1):** 21-40.

[1]MBBS, MD, Assistant Professor, Department of Community Medicine, KPC Medical College, Kolkata 700075 — **Dhaval Parekh**[1]
[2]MBBS, Student, BJ Medical College, Ahmedabad 380016 — **Tattvam Gaurang Shah**[2], **Vedanti Kavin Dave**[2]

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION :
Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014
Phone : (033) 2237- 8092, Mobile : +919477493027; E-mail : jima1930@rediffmail.com
Website : https://onlinejima.com ; www.ima-india.org/ejima
Head office : Indian Medical Association, IMA House, Indraprastha Marg, New Delhi - 110 002
Telephones : +91-11-2337 0009, 2337 8680, Email : hsg@ima-india.org : Website : www.ima-india.org

Registration No. KOL RMS / 476 / 2023 - 2025

RNI Regd. No. 2557/1957
Vol. 67, No. 10, October 2023, Kolkata

Date of Publication : 20th October, 2023

If not delivered please return to
Journal of the IMA (JIMA)
53, Sir Nilratan Sarkar Sarani,
(Creek Row), Kolkata - 700014

Printed and Published by **Dr Jyotirmoy Pal** on behalf of Indian Medical Association and printed at Prabaha, 45, Raja Rammohan Sarani, Kolkata - 700009 and Published from Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata 700014, Editor : **Dr Tamonas Chaudhuri**