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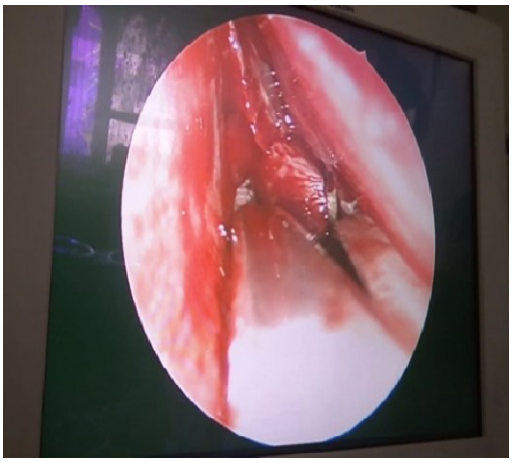
Removal of spur with Lucs forceps in Endoscopic surgery



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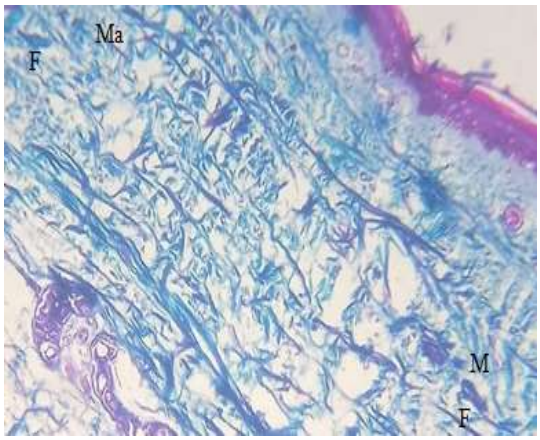
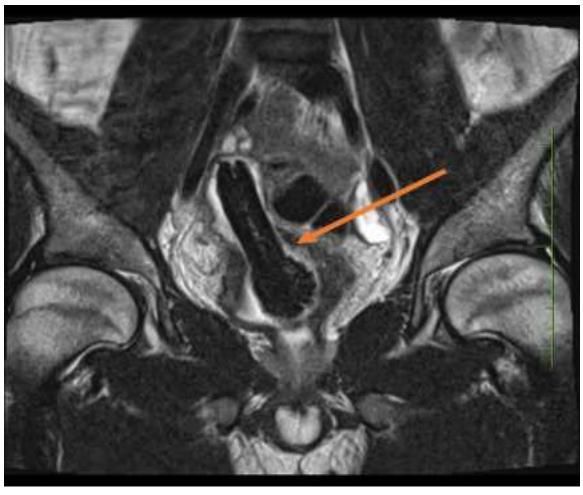


Show a well circumscribed hypodense mass

MRI showing elongated foreign body



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EDITORIAL

Personalized Medicine and Future of Surgical Planning: Metaverse, Virtual Surgeries & Surgical Planning with the Use of Digital Twinning

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Surgical planning is one of the most promising areas where Digital Twins (DTs), the metaverse, virtual surgeries, and personalized medicine and surgery intersect to revolutionize patient care. These technologies enable more precise, efficient, and safer surgical procedures while also allowing for personalized treatment tailored to each patient's specific needs. These concepts are applied in surgical planning and the execution as follows:

Digital Twinning in Surgical Planning

A Digital Twin is a virtual representation of a patient's anatomy, created using data from various sources such as medical imaging (CT scans, MRIs), genetic information, and real-time monitoring through sensors or wearables. This digital model allows surgeons to simulate and plan surgeries with incredible precision before making any incision. Key aspects include:

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- *Personalized Anatomy Models:* By creating a detailed, patient-specific Digital Twin, surgeons can have an accurate 3D model of the patient's organs, tissues, and bone structure. This allows them to study the specific anatomical features of the patient in detail, identifying potential challenges or abnormalities that may not be visible on standard imaging.
- *Pre-Surgical Simulation:* Surgeons can virtually rehearse the procedure in a simulated environment, testing various approaches and strategies. This reduces the likelihood of unexpected complications during actual surgery and increases the overall success rate.
- *Predictive Analytics:* The Digital Twin can be used to predict the outcomes of various surgical approaches, helping to select the most effective treatment strategy. For example, it can simulate how tissues will respond to different surgical techniques or post-operative care, optimizing the recovery process.

The Metaverse in Surgical Planning and Training

The metaverse—a shared, immersive, virtual environment where people can interact with digital twins and other virtual representations—can significantly enhance surgical planning and training.

- *Immersive Surgical Simulations*: Surgeons can use the metaverse to enter an immersive environment where they interact with the Digital Twin of a patient. This allows them to visualize the anatomy from different angles, practice the surgery multiple times, and experiment with different techniques in a risk-free virtual setting. For complex surgeries, like brain or heart surgery, this has becomes invaluable for honing skills and understanding the nuances of individual cases.
- *Collaborative Surgery Planning:* The metaverse can connect surgeons from around the world in a collaborative, virtual space. Surgeons can discuss surgical approaches, share insights, and participate in joint decision-making, all while interacting with the Digital Twin of the patient. This enhances the exchange of expertise, especially for rare or complex conditions.
- *Patient Education and Involvement:* Patients can also enter the metaverse to interact with their own Digital Twin. By visualizing their surgery and recovery process in 3D, they can better understand the procedure, ask questions, and feel more involved in their care decisions. This enhances patient satisfaction and engagement in the treatment process.

Virtual Surgeries & informed decision-making during surgery

Virtual surgeries are becoming a powerful tool for both pre-surgical planning and real-time surgical support.

- *Virtual Reality (VR) Surgery Practice:* Surgeons can practice and refine their skills using VR platforms that replicate real-world surgical environments. These virtual surgeries allow surgeons to rehearse techniques, familiarize themselves with the anatomy, and optimize their approach before performing the actual surgery.
- *Real-Time Guidance during Surgery:* During actual surgery, the surgeon can access real-time data from the patient's Digital Twin. For example, augmented reality (AR) overlays can be used during the procedure, showing critical information such as the location of blood vessels or tumors that may not be immediately visible. This provides enhanced precision and supports more informed decision-making during the surgery.
- *Robotic-Assisted Surgery:* Virtual surgery technology is closely tied to robotic surgery systems. Surgeons can control robotic instruments through virtual interfaces, allowing for highly precise and minimally invasive procedures. Robotic systems can integrate data from Digital Twins to adjust the operation based on real-time feedback, ensuring optimal outcomes.

Personalized Medicine and Surgery

Personalized medicine relies on genetic, molecular, and clinical data to create more effective treatments with fewer side effects. This refers to tailoring medical treatments to the individual characteristics

of each patient. In surgery, this concept extends to personalized surgical planning:

- *Tailored Surgical Approaches:* Each patient's unique anatomy, medical history, and genetic predispositions can affect how they respond to surgery. Surgeons can customize the surgical approach using a Digital Twin based on the patient's specific needs, such as considering potential complications, surgical risks, or recovery trajectories. For example, a surgeon might select a less invasive technique for a patient with a specific genetic marker that indicates a higher risk for scarring or tissue damage.
- *Optimized Recovery Plans:* Digital Twins can continue tracking a patient's recovery after surgery, providing personalized post-operative care recommendations. By simulating how a patient's body is healing and adjusting based on real-time data, healthcare providers can optimize recovery plans to prevent complications such as infections, blood clots, or improper healing.
- *Genomic Data Integration:* Personalized medicine in surgery can also extend to the use of genomic data. For example, specific gene mutations can influence how a patient responds to anesthesia, heals after surgery, or recovers from certain treatments. This data can be integrated into the Digital Twin to create a comprehensive, predictive model that informs surgical strategies.

Future Outlook: Advanced Applications and Integration

While these technologies are still developing, the future of surgical planning holds immense potential:

- *Predictive Surgery:* With further advancements in AI and data analytics, Digital Twins will be able to not only simulate surgeries but predict outcomes in real-time, adjusting for changes in the patient's condition, treatment response, and recovery progress.
- *Integrating Multi-Disciplinary Expertise:* Digital Twins and the metaverse could integrate input from various specialties—such as cardiology, neurology, and oncology—into a unified surgical plan, ensuring comprehensive and highly specialized care for complex conditions.
- *Personalized Implants and Devices:* For some surgeries, especially orthopedic or reconstructive procedures, Digital Twins can help design custom implants or devices tailored to a patient's anatomy specifications. This ensures a better fit and faster recovery.

Thus, the integration of Digital Twins, the metaverse, virtual surgeries, and personalized medicine is transforming the landscape of surgical planning and execution. By providing surgeons with detailed, patient-specific models, enhancing surgical training, and enabling real-time decision support during procedures, these technologies are setting the stage for more precise, effective, and personalized surgical interventions. As these innovations continue to evolve, the future of surgery holds the promise of even more refined, data-driven, and patient-centered care.

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ORIGINAL ARTICLE

A Comparative Study of Conventional vs. Endoscopic Septoplasty

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Abstract

Background: Septoplasty is the treatment for the symptomatic Deviated Nasal Septum. There has been a drift from septal resection to mucosal preservation to conservation of possible septal framework in the septoplasty surgeries. The endoscopic technique is modern evolution of the septoplasty surgery. This study has been undertaken to evaluate the conventional and endoscopic approaches of the septoplasty surgeries and aid in statistical informative data to ongoing researches for better outcome comparison. **Aims and Objectives:** To compare conventional and endoscopic techniques of Septoplasty and to find out which technique is better on the basis of various intraoperative and postoperative objectives. **Material and Methods:** A prospective randomized comparative study was conducted with a sample size of total 60 patients; 30 in each group. Both the groups were statistically compared for various predefined intraoperative and postoperative objective to determine the better technique of septoplasty. **Results:** Endoscopic technique was better than conventional in terms of ease for surgical process, time taken for the surgery, intra operative blood loss, visualization of the pathology and postoperative residual deviation. **Conclusions**: Endoscopic technique was found better in terms of less intra operative complication like bleeding, better visualization, better illumination, magnification, more conservative approach, ease of surgery, less time duration of surgery and less postoperative residual deviation with limitation of binocular vision and bimanual work. Endoscopic septoplasty is modern alternative technique to conventional septoplasty and is a good teaching tool also.

Keywords: Septoplasty, Endoscopic Septoplasty, Conventional Septoplasty, Comparative study

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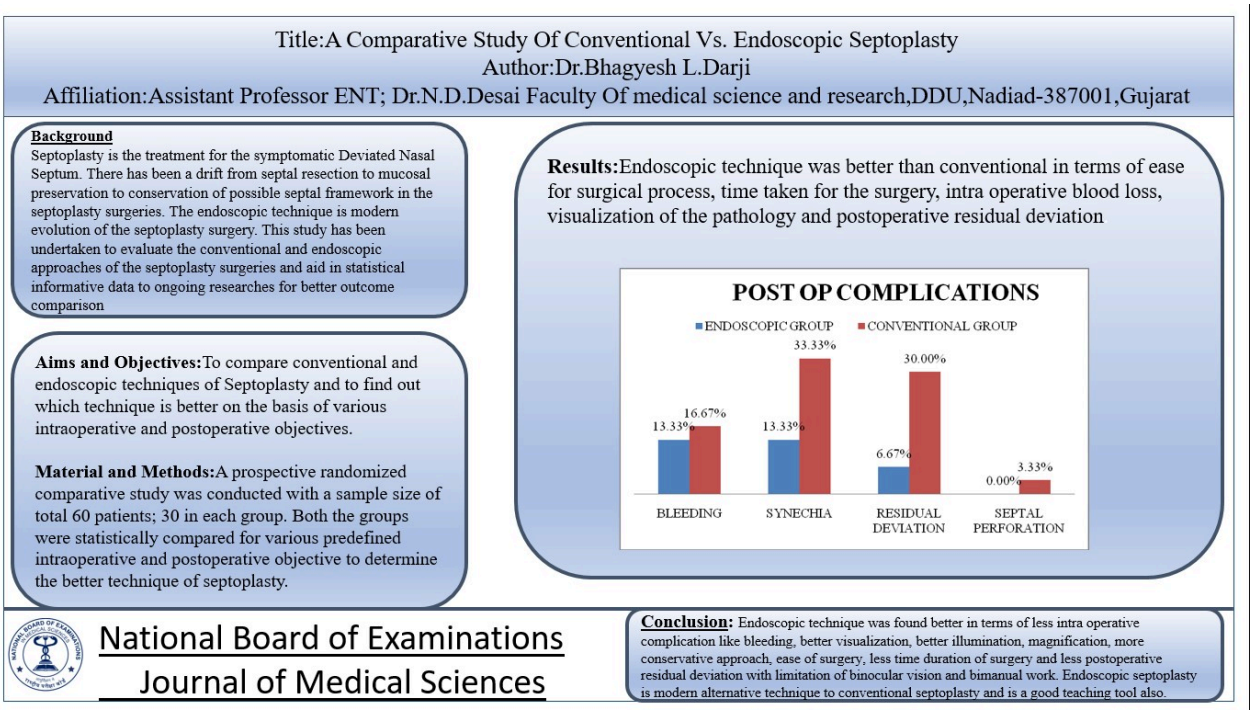
Graphical Abstract



Abbreviations

ENT : Ear, Nose, Throat
OPD: Out Patients Department
DNS : Deviated Nasal Septum
BC : Before Christ
SMR : Submucosal Resection
DNE :Diagnostic Nasal Endoscopy
VAS :Visual Analogue Scale

Introduction

Treatment for the Deviated Nasal Septum is Septoplasty. It can be performed either conventionally using the headlight or with the visualization on a monitor using Nasal Endoscopes. In the current era of newer surgical instruments, technologies and emphasis on saving the normal anatomical structures and preservation of normal mucosa with the removal of most deviated parts and correcting the pathological part only is being exercised. There has been a drift from septal resection to mucosal preservation to conservation and preservation of possible septal framework in the septoplasty surgeries [1]. The endoscopic technique is modern evolution of the septoplasty surgery. There are group of surgeons performing the septoplasty surgery conventionally using headlight and another using the endoscopes for the same. The debate and research regarding the better technique for the septoplasty is going on. This study has been undertaken to evaluate the conventional and endoscopic approaches of the septoplasty surgeries and aid in statistical informative data to ongoing researches for better outcome comparison.

Aims and Objectives

To compare conventional and endoscopic techniques of Septoplasty and to find out which technique is better on the basis of following parameters:

A) Intra operative

1. Ease of process (Easy/Difficult)
2. Time duration of Surgery(In minutes)
3. Intraoperative complications:-
    a. Bleeding(Amount of suctioned blood in milliliters)
    b. Mucosal Flap Tear (Present/Absent)
4. Visualization of Pathology/deviation (Satisfactory/Unsatisfactory)

B) Postoperative complication (Present/Absent)

1. Bleeding
2. Synechia
3. Residual deviation
4. Perforation

C) Postoperatively symptoms relieved (Visual Analogue Scale)

1. Nasal obstruction
2. Headache
3. Nasal discharge
4. Postnasal drip
5. Hyposmia
6. Epistaxis

Material and Methods

Study Population

Patients attending ENT OPD diagnosed to have symptomatic Deviated Nasal Septum on the basis of detailed clinical history and clinical and radiological examination which needs correction with given consent.

Sample size

Total 60 patients in this study divided in endoscopic and conventional groups, 30 in each group by simple randomization method using table of random numbers.

Study Design

Prospective randomized cohort study.

Inclusion Criteria

I. All patients diagnosed to have symptoms due to deviated Nasal Septum on the basis of clinical evaluation above the age of 18 years and with patients consent for being included in the study group.

II. All patients of chronic Rhinosinusitis not responding to conservative management having associated Deviated Nasal Septum of magnitude interfering with endoscopic sinus surgery.

Exclusion Criteria

I. Patients under the age of 18 years.
II. Revision Septoplasty.

Methodology

Patients attending ENT OPD with symptomatic deviated nasal septum evaluated with detailed clinical history and examination. Those patients diagnosed to have deviated nasal septum requiring correction and willing to undergo septoplasty were included in the study.

Preoperative symptoms and clinical findings were recorded accordingly. DNE done with 0* rigid 4mm endoscopes and findings were recorded. Visual analogue scale used to record the presenting symptoms severity. Patients requiring surgery for the symptomatic deviated nasal septum identified according to inclusion and exclusion criteria and preoperative workup for the surgery done with required blood,

urine and radiological investigation and anaesthetic fitness obtained for general/local anaesthesia.

Patients undergoing surgery randomized into Group A (undergoing conventional septoplasty), and Group B (undergoing endoscopic septoplasty) using table of random numbers.

All the surgeries were performed under local anesthesia with sedation.

Ethical clearance was obtained from the institutional ethical committee.

Technique for Conventional Septoplasty

For the conventional Septoplasty, nasal cavities packed with 4% Lignocaine and Xylometazoline 0.1% soaked cotton packs for 10-15 minutes while patient lying supine. 1 ml Pentazocin and 1 ml Phenargan in 3 ml sterile water given intravenously. Painting followed by draping done. Head light used. Local 2%Lignocaine with 1 in 1 lakh Adrenaline solution infiltrated in columella, either side of septum, over spur (if any) and maxillary crest.

Surgery performed with Headlight. Killian`s incision was given on left side of septum despite of side of deviation and mucoperichondrial and mucoperiosteal flaps elevated with the help of Freer's elevator and Killian`s long bladed nasal speculum. Anterior, posterior, inferior and opposite side anterior tunnels made. Oseo-cartilagenous junction dislocated and opposite side posterior tunnel made. Small part of perpendicular plate of ethmoid was fractured and removed with Luc`s forceps.

Then about 0.5 cm inferior strip cartilage was removed. Spur if any removed and maxillary crest spur if found was removed with the help of gouge and mallet. Haemostasis achieved with suction and Neuropatties soaked in 4%lignocaine and adrenaline solution. Sutures taken at incision site with 4-0 vicryl. Any mucosal flap tear if present recorded. Amount of suction blood recorded from marked collector attached with it.

Both the Nasal Cavities were packed with soframycin soaked ribbon packs. Bolster dressing applied. Time duration of surgery was noted from local infiltration to bolster dressing. Ease of surgery (easy or difficult) and visualization of pathology (satisfactory or unsatisfactory) noted for every case.

Technique for Endoscopic Septoplasty:

Nasal cavities packed with 4% Lignocaine and Xylometazoline 0.1% soaked cotton packs for 10-15 minutes. 1ml Pentazocin and 1ml Phenargan in 3ml sterile water was given intravenously. Painting followed by draping done. Local 2% Lignocaine with 1 in 1 lakh Adrenaline solution infiltrated in columella, either side of septum, over spur (if any) and maxillary crest using 0*,4 mm endoscope connected to a monitor.

Vertical incision made just caudal to the deviated portion of the septum on convex side and extended both superior and inferiorly for the better exposure.

Mucoperichondrial flap raised using Freer`s elevator with visualization with 0 degree rigid 4 mm nasal endoscope.

The incision was given on deviated part of cartilage parallel, but posterior to flap incision and caudal to deviation. Then Freer's elevator was inserted and mucoperichondrial flap was raised on opposite side.

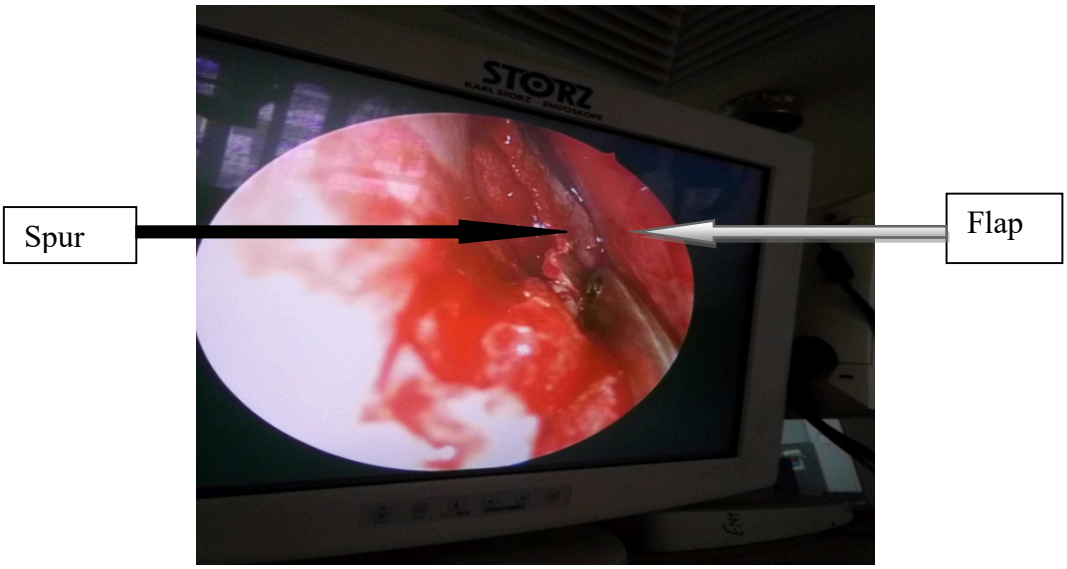


Figure 1. Endoscopic mucoperichondrial flap elevation and showing spur

Luc's forceps was used to excise the deviated part of septum.

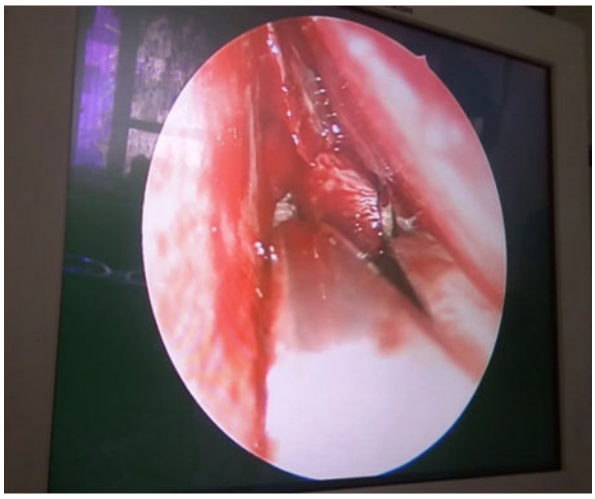


Figure 2. Removal of spur with Lucs forceps in Endoscopic surgery

In Cases of maxillary crest deviation, elevation of flaps over crest done under endoscopic vision and deviated parts were removed with gouge and hammer.

In cases of isolated spur, incision was given directly over the spur under endoscopic view, flaps elevated superior and inferiorly and spurs removed.

Haemostasis achieved with suction and neuropatties soaked in 4% lignocaine and adrenaline solution. Sutures were taken at incision site with 4-0 vicryl. Any mucosal flap tears if present, recorded. Amount of

suction blood recorded. Both the Nasal Cavities were packed with soframycin soaked ribbon packs. Bolster dressing applied.

Time duration of surgery was noted from local infiltration to bolster dressing. Ease of surgery (easy or difficult) and visualization of pathology (satisfactory or unsatisfactory) noted for every case.

Postoperative Care and Follow Up:

Patients were given same antibiotics, analgesics and antihistaminic in post op periods in both the groups.

Nasal packs were removed on 2nd post operative day and discharged with advice, oral medications and topical nasal sprays.

Patients were followed up on 7th, 14th, 30th and 60th post operative days. In each visit examination and suctioning done and improvement in presenting symptoms were noted on Visual Analogue Scale.

In each visit DNE was performed and Postoperative complications like bleeding, abscess, haematoma, synechia, residual deviation and septal perforation if any noted. Thus the objective and subjective data of symptoms relieved and post operative complications were obtained.

Data Analysis

Data thus obtained was analysed using SPSS software.

Post operative symptomatic improvement in subjective criteria via VAS score were analyzed by Standard error of mean using Student's 't' test.

Subjective intra operative criteria like ease of surgery and visualization of pathology were analyzed by comparing standard error of proportion of two groups using Chi square test.

Objectives like time duration of surgery and bleeding during surgery were compared with 't' test.

Post operative complications in both groups were compared and analysed by standard error of proportions applying Chi square test.

All statistical analysis were carried out at 95% confidence level, α =5% and 80% power; to test the alternate and null hypothesis and to rule out occurrence of events by chance between Group A (underwent Conventional septoplasty) and Group B (underwent Endoscopic septoplasty).

Results

As per the study to evaluate the conventional and endoscopic techniques of the septoplasty surgery on the basis of intra and post operative subjective and objective criteria, which were evaluated statistically, got the following results:

Intra Operative Evaluation

Table 1. Intra operative objectives compared between conventional and endoscopic techniques

Objectives	**Conventional**	**Endoscopic**	**P Value**	**Significance**
Ease of process	43.33%(EASY)	70.00%(EASY)	0.037	Significant
Time duration(MEAN)	51.53 minutes	49.90 minutes	0.020	Significant
Blood Loss(MEAN ml)	20.97 ml	19.20 ml	0.007	Significant
Mucosal Flap Tear	36.66%	16.66%	0.08	Non Significant
Satisfactory Visualization of Pathology	53.33%	96.67%	0.000	Significant

Table 1 shows the intra operative objectives which were compared between conventional and endoscopic techniques. The endoscopic technique was found easy in 70% cases compared to 43.33% in conventional group with p value of 0.037, which is statistically significant.

The time duration for surgery was 49.90 minutes in endoscopic group compared to 51.53 minutes in conventional group with p value of 0.020, which is statistically significant.

The mean blood loss was 19.20 ml in endoscopic group as compared to 20.97 ml in conventional group with significant p value of 0.007.

The frequency of mucosal flap tear was 16.66% in endoscopic group compared to 36.66% in conventional group with p value more than 0.05 which was statistically insignificant.

In endoscopic group 96.67% cases had adequate visualization of pathology while 53.33% in conventional group had satisfactory visualization of pathology during surgery with statistically significant p value of 0.000.

As per the statistical analysis the study showed that endoscopic technique was better than conventional in terms of ease for surgical process, time taken for the surgery, intra operative blood loss and visualization of the pathology.

There was no difference found in incidence of mucosal tear during surgery by either technique.

Post Operative Evaluation

Table 2. Frequency of post operative complications in both the groups.

Complication	Endoscopic Group	Conventional Group	P Value	Significance
Bleeding	13.33%	16.67%	0.718	Non Significant
Synechia	13.33%	33.33%	0.067	Non Significant
Residual Deviation	6.67%	30.00%	0.02	Significant
Septal Perforation	0.00%	3.33%	0.313	Non Significant

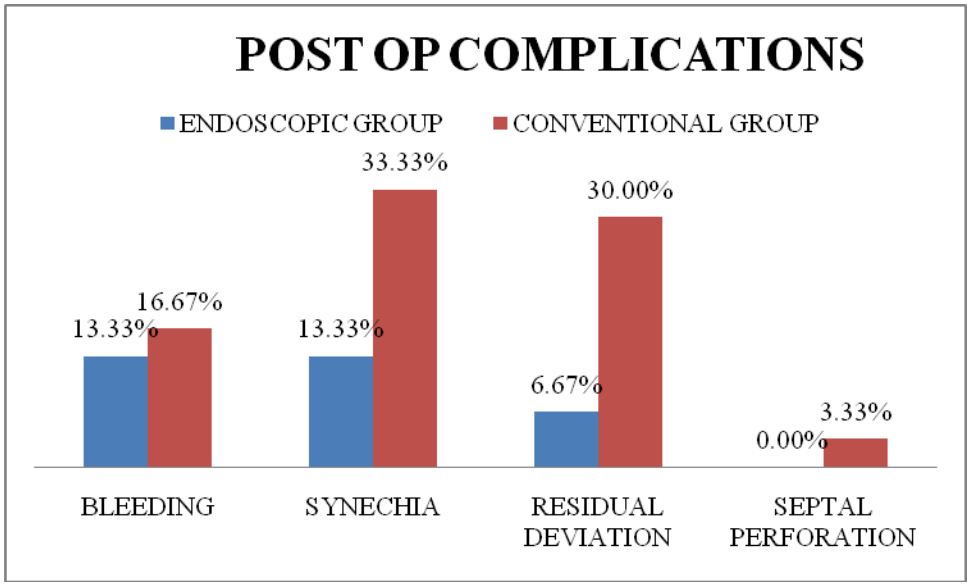


Figure 3. Frequency of post operative complications in both the groups.

Table 2 and Figure 3 describe the frequency of post operative complications in both the groups. Post operative bleeding was found in 13.33% cases in endoscopic group as compared to 16.67% in conventional group with p value of 0.718, which is statistically insignificant.

Synechia was found in 13.33% cases in endoscopic group, while in conventional group it was found in 33.33% cases with statistically insignificant p value of 0.067.

The residual deviation was found in 6.67% cases in endoscopic group as compared to 30% in conventional group with statistically significant p value of 0.02. No septal perforation was found in endoscopic group, while 3.33% patients in conventional group had septal perforation with p value of 0.313, which is statistically insignificant.

This analysis depicts that neither technique was superior in terms of post operative bleeding, synechia formation and septal perforation. The endoscopic surgery was found better in terms of having less post operative residual septal deviation.

Post Operative Symptomatic Improvement

Table 3. Results of Postoperative Symptomatic Improvement

Symptoms	p Value	Significance
Nasal Obstruction	.825	Non Significant
Headache	.814	Non Significant
Epistaxis	.298	Non Significant
Nasal Discharge	.170	Non Significant
Post Nasal Drip	.533	Non Significant

Table 3 signifies that both techniques were equivalent in terms of relieving symptoms post operatively. In this study there was no statistically significant difference found in post operative subjective symptomatic improvement in nasal obstruction, headache, epistaxis, nasal discharge and post nasal drip.

Thus, study results showed that endoscopic technique was better than conventional technique in following aspects:

a. Ease of process,
b. Time duration of surgery,
c. Intra operative blood loss,
d. Visualization of pathology during surgery and
e. Post operative residual deviation.

Both techniques were similar in following aspects:

a. Intra operative mucosal flap tear,
b. Post operative complications like bleeding, synechia, septal perforation and
c. Post operative symptomatic improvement.

Discussion

Septoplasty was first described by Cottle in 1947 as a treatment to correct nasal airway obstruction [2]. Lanza et al. described endoscopic techniques to correct septal deformities [3].

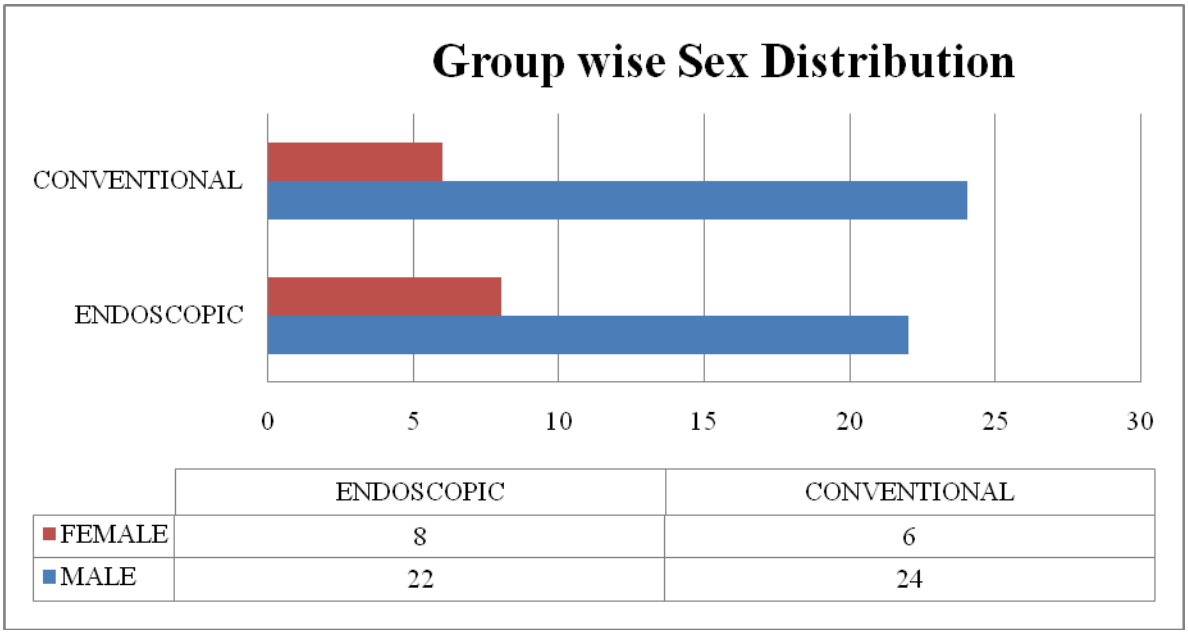
According to Brennan et al. the ideal objective in septal surgery is permanent correction of deviation with avoidance of any complication [4].

Endoscopic septoplasty is an attractive alternative to traditional headlight approach for surgery. Early reports of endoscopic septoplasty describe several advantages associated with the technique e.g. it makes easier for surgeons to see the tissue planes and it offers a better way to treat isolated septal spurs. Additionally, the endoscopic approach makes it possible for many people to simultaneously observe the procedure on a monitor, making the approach useful in a teaching hospital. The

main disadvantages of endoscopic septoplasty are contamination of the endoscope with blood, which obscures the endoscope view and repeated cleaning. Also, as one hand is occupied holding the nasal endoscope, other instruments must be manipulated with a single hand, which may be difficult at times [5].

Deviated nasal septum related to Sex

There was male preponderance in having DNS than females; ratio for conventional group was 4:1 (Male:Female) and for endoscopic group it was 2.75:1 as shown in Figure 4. This is in accordance to the literature saying Males have more preponderance to have DNS [6-11].



	ENDOSCOPIC	CONVENTIONAL
FEMALE	8	6
MALE	22	24

Figure 4. Group wise sex distribution

Deviated nasal septum related to Side

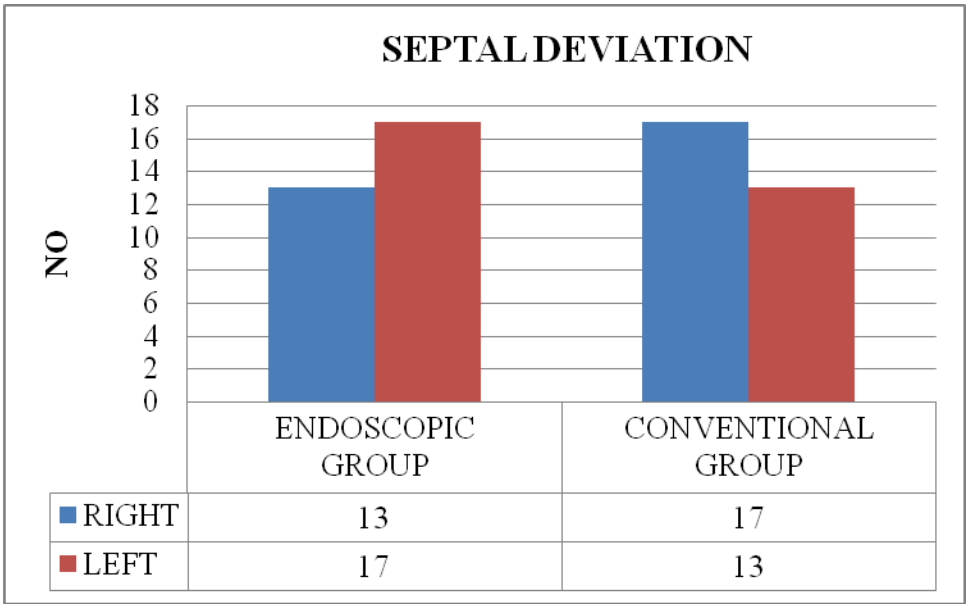


Figure 5. Deviated nasal septum related to Side:

In this study as shown in Figure 5, equal numbers of right and left deviated nasal septum were found which does not conform to the literature which states that left is more common than right [12,13].

Deviated nasal septum related to Presenting Symptoms:

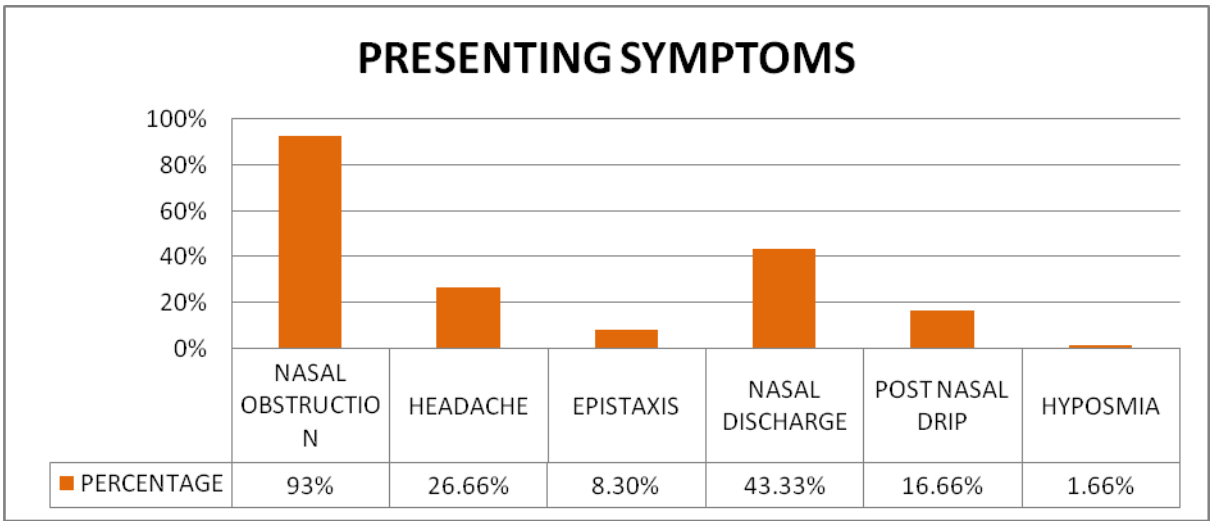


Figure 6. Deviated nasal septum related to Presenting Symptoms

Regarding presenting symptoms as shown in Figure 6, Nasal obstruction was the leading complaint (93%) which is found in the studies done by Khan et al.; Verma et al; Leen et al; Gupta and Motwani [8,12,13].

Other complaints were Headache (26.66%), Nasal discharge (43.33%), post nasal drip (16.66%) and Hyposmia (1.66%). These findings are in concordance to the study by Leena at al. and Gulati et al. [8,14].

Ease of Process

In our study, according to performing surgeons perception 70.00% endoscopic surgery were found easy and 43.33% conventional surgery found to be easy to perform. This may be related to the better visualization and illumination which can be achieved by the endoscopes and limited, obstructed vision while performing conventional septoplasty using headlight and nasal speculums.

Time Duration of Surgery

The average time taken to perform conventional surgery was 51.53 minutes and that of endoscopic was 49.90 minutes. The p value was 0.02 which is statistically significant and showed that endoscopic surgeries were faster to perform and saved time. This finding is in agreement with the authors Giles et al; Horry et al. and Shehata et al. where endoscopic surgery vary from 15 to 27 min. while conventional took 23 to 34 min [10,15,16].

Khan et al. found endoscopic surgeries took longer than conventional. Time for conventional septoplasty was 36.35 min. with a standard deviation of ±5.33 min and for endoscopic septoplasty, the mean intra-operative time was marginally more being 38.7 min. with a standard deviation of ±4.77min [13].

Intra Operative Blood Loss

Mean blood loss in conventional group was 20.97 ml and in endoscopic group was 19.20 ml. The p value was 0.007, which signified that endoscopic technique was better than conventional surgery in terms of intra operative blood loss.

Intra Operative Mucosal Tear

Mucosal flap tear was present in 36.66% patients in conventional group and 16.66% in endoscopic group. Though the frequency of mucosal flap tear during operation was less in endoscopic group than conventional, it was not statistically significant. This is in concordance to the study done by Sathyaki et al. and Yadav et al. and against the study done by Paradis et al. [9,11,17].

Visualization of Pathology

In this study, endoscopic surgery provided 96.67% satisfactory visualization of deviated septum as spur, posterior and anterior deviations and high and low deviations. In conventional group only 53.33% satisfactory visualization of pathology accessed. It was statistically highly significant (p=0.000). This can be attributed to better illumination, better access to the various portions of septum and ability to manipulate and observation on monitor as described in literature by Leena et al; Sathyaki et al; Verma et al; Khan et al; Gulati et al and Kapil et al. [8,9,12-14,18].

Subjective Improvement in VAS score

In this study, in the both groups, there was statistically significant improvement in presenting symptoms post operatively except for epistaxis, but neither technique was better in post operative symptomatic improvement based on VAS score, as the p value for the test of significance was >.05, as illustrated in Table 3. This disagrees with Leena et al. [8] Khan et al. [13]. This study is in concordance with the study by Shehata A et al. which showed significant improvement in headache, epistaxis and facial pain but no significant improvement in nasal obstruction, post nasal discharge or hyposmia [10].

Postoperative Complications

Postoperative complications were evaluated objectively. DNE was performed and findings were noted for residual deviation, synechia and septal perforation.

Table 4. Comparison of post-operative complications of conventional septoplasty in present study with various previous studies

	Leenajain et al.[8]	Sathyaki et al.[9]	Shrestha et al.[19]	Suligavi et al.[20]	Kamran et al.[21]	Manjunath et al.[22]	Khan MN et al.[13]	Present study
Bleeding	-	24%	-	26%	3%	4%	6.67%	16.67%
Residual Deviation	36%	-	17.2%	14%	2%	-	36.67%	30%
Synechia	20%	16%	16.6%	20%	1%	4%	16.67%	33.33%
Septal Perforation	-	-	10%	-	2%	0%	6.67%	3.33%

Table 4 shows the comparison of the post operative complications of the conventional septoplasty between this study and previous studies.

Table 5. Comparison of post-operative complications of endoscopic septoplasty in present study with various previous studies

	Leenajain et al.[8]	Shrestha et al.[19]	Suligavi et al.[20]	Manjunath et al.[22]	Chung et al.[23]	Khan MN et al.[13]	Present study
Bleeding	-	-	14%	4%	0.9%	0%	13.33%
Residual Deviation	13%	10%	16%	-	0.9%	6.67%	6.67%
Synechia	0%	6.7%	6%	4%	2.6%	6.67%	13.33%
Septal Perforation	-	0%	-	0%	3.4%	0%	0%

Table 5 shows the comparison of post operative complications of endoscopic septoplasty between the present and previous studies.

Endoscopic septoplasty can also be considered an effective teaching tool. In fact, when viewed over a monitor, the procedure provides an excellent opportunity for recording and studying anatomy, pathology and surgical techniques in the training of Assisting Surgeons, graduate Specialists and Medical students [8].

Conclusion

To conclude, both the techniques give satisfactory post operative results and can be performed to correct symptomatic deviated nasal septum. Endoscopic technique is found better in terms of less intra operative complication like bleeding, better visualization, better illumination, magnification, more conservative approach, ease of surgery, less time duration of surgery and less post operative residual deviation with limitation of binocular vision and bimanual work. Endoscopic septoplasty is modern alternative technique to conventional septoplasty and is a good teaching tool also.

Ethical Approval

The study got approval from Institutional Scientific Review (SRC) Committee and Institutional Ethic Committee (IEC)

Informed Consent

Informed written consent was obtained from the patient/participants

Conflicts of Interest

The authors declares that they do not have conflict of interest.

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ORIGINAL ARTICLE

A Study on Assessing the Diabetic Risk Among Health Care Professionals in a Tertiary Care Hospital, Puducherry: A Cross-Sectional Study

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Abstract

Introduction: Diabetes is a chronic metabolic disorder marked by elevated blood glucose levels, with type 2 diabetes being the most prevalent form. As a non-communicable disease, diabetes poses a major public health challenge, and its prevalence is rising worldwide, reaching epidemic levels that may soon surpass those of communicable diseases in both developing and developed countries. **Objective:** To evaluate the risk of diabetes among doctors and nurses at a tertiary care hospital. **Methodology**: A hospital-based cross-sectional study was carried out among doctors and nurses at a tertiary care hospital in Puducherry from February to April 2022. Participants for the survey were selected using a simple random sampling method. **Results:** Most participants in the study were aged between 36 and 49 years, comprising 60.5% of the sample. Among them, 63.0% were male, and 65.5% resided in urban areas. The largest proportion had a normal BMI (51.5%), followed by overweight individuals (36.5%) and those classified as obese (7.5%). Additionally, 59.5% of participants exhibited abdominal obesity, 63.5% reported no physical activity, and 77.5% did not have a family history of diabetes. **Conclusion:** This study evaluates the effectiveness of a simplified Indian Diabetes Risk Score (IDRS) in identifying high-risk individuals within the working population. There is an immediate need to encourage for healthy lifestyle practices among doctors and nurses. Physicians should actively strive to implement the knowledge they possess daily.

Keywords: Blood glucose, Type 2 diabetes, Diabetes mellitus, Indian Diabetes Risk Score

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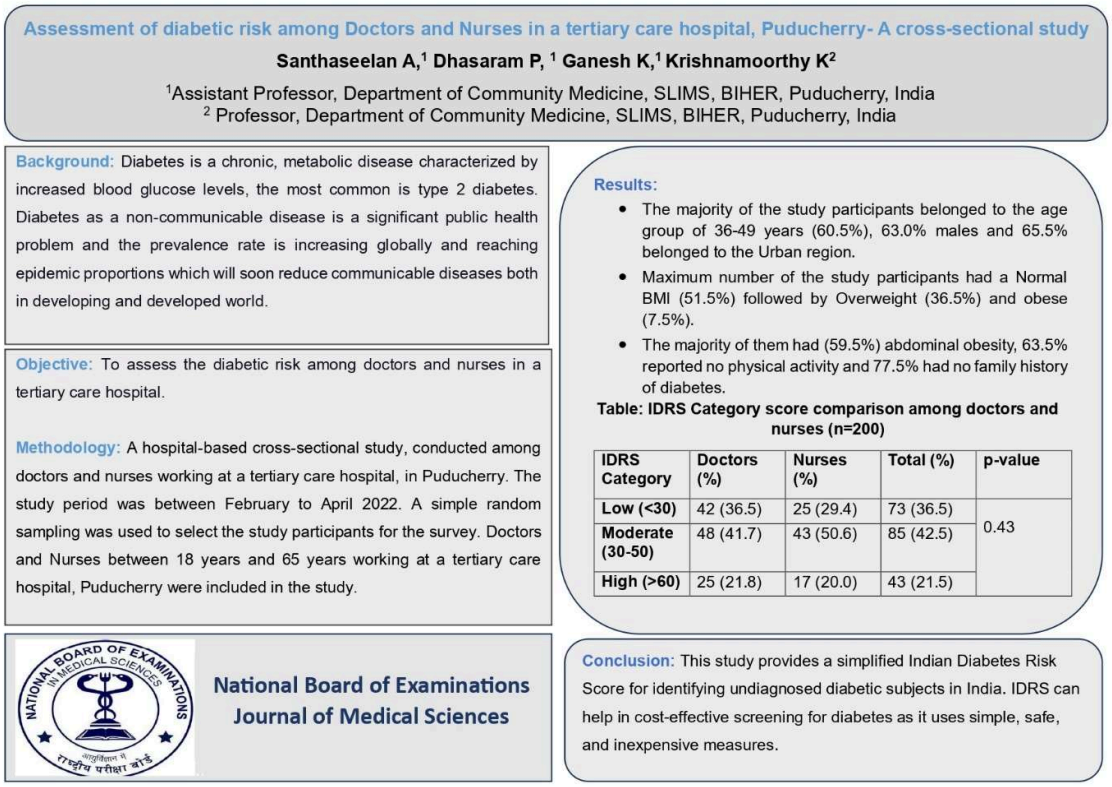
Graphical Abstract



Introduction

The world is currently grappling with a surge in non-communicable diseases (NCDs), with diabetes standing out as a major public health challenge due to its increasing prevalence globally. Diabetes is a chronic metabolic disorder defined by elevated glucose levels in the blood, primarily manifests as type II diabetes mellitus, which has become particularly common [1,2].

In India, the prevalence of diabetes among individuals aged over 45 was reported at 11.5% in 2021, as per a study by the Ministry of Health and Family Welfare. The country faces a significant burden of diabetes due to genetic predisposition and heightened susceptibility to environmental factors [3,4]. Recent data from the Indian Council of Medical Research underscores this, revealing an overall diabetes prevalence of 7.3% across 15 states [5].

Healthcare providers, such as doctors and nurses, play a crucial role in public health by ensuring the well-being of individuals. Their own health is vital as it directly impacts their ability to perform effectively in demanding work environments. Research indicates a strong link between healthcare providers' personal health choices and their advice to patients [6].

While doctors and nurses are expected to possess sound knowledge of cardiovascular diseases (CVDs), diabetes, and associated risk factors, their lifestyle habits often present challenges, they frequently lead sedentary lives, experience high stress levels, lack adequate rest, and have irregular eating patterns, predisposing them to diabetes and CVDs [7,8]. The

study was determined to assess the diabetic risk among healthcare professionals in a tertiary care hospital, Puducherry.

Methodology

The current study was a hospital-based cross-sectional investigation conducted among doctors and nurses at a tertiary care hospital in Puducherry. Data for the study were collected between February and April 2022. The sample size was determined using Cochran's formula $n= Z^2 pq / d2$ with a diabetes prevalence of 13.0% among health workers based on previous research and d=5. This calculation yielded a total sample size of 181, which was adjusted to 200 to account for a 10% non-response rate. A simple random sampling method was used to select the study participants.

Eligibility criteria

Inclusion criteria

Healthcare professionals, those aged 18-60 years working at the tertiary care hospital.

Exclusion criteria

- Visiting doctors
- Those who joined within the past year

Data collection tool

Written informed consent was obtained from all participants involved in the survey. A semi-structured questionnaire was used to interview the study participants. The following information obtained includes socio-demographic details and questions aimed at assessing the diabetes risk among healthcare professionals in a tertiary care hospital. Data like blood pressure, blood glucose levels, and anthropometric measurements were also collected. The cut-off values for the Waist-Hip Ratio (WHR) used to define central obesity were >0.85 for females and >0.9 for males. Participants with an IDRS score of < 30 were classified as low risk, those scoring between 30 to 50 were considered medium risk, and individuals with scores of 60 or higher were categorized as high risk. Participants with a diabetes risk score more than 30 were recommended to visit a hospital for blood sugar testing and follow-up.

Data analysis

The data collection form was assessed for valid entries and missing entries. Data entry was made in MS EXCEL 2019. Data coding was done in MS Excel and analyzed using IBM SPSS software version 16.0, Chicago, USA. Normally distributed values were presented as mean ± standard deviation whereas non-normally distributed values were presented as median. Categorical values were presented as proportions.

Results

The current study involved 200 participants at a tertiary care hospital in Puducherry. Most participants were in the age group of 36-49 years (60.5%), with 126 males and 74 females. Among the 200 participants, 89.5% identified as Hindus, 79.5% lived in nuclear families, and 65.5% resided in urban areas (Table 1). The largest group had a normal BMI (51.5%), followed by overweight individuals (36.5%) and those classified as obese (7.5%). Additionally, 59.5% of participants had abdominal obesity, 63.5% reported no physical activity, and 77.5% had no family history of diabetes (Table 2).

Table 1. Socio-demographic characteristics of the study participants (n=200)

Characteristics	Number (n)	Percentage (%)
Age Group		
<35	70	35.0
36-49	121	60.5
>50	9	4.5
Sex		
Male	126	63.0
Female	74	37.0
Religion		
Hindu	179	89.5
Muslim	13	6.5
Christian	8	4.0
Family type		
Nuclear	159	79.5
Joint	41	20.5
Place of residence		
Urban	131	65.5
Rural	69	34.5

Table 2. Factors associated with increased risk of diabetes among study participants (n=200)

Characteristics	Number (n)	Percentage (%)
BMI		
Underweight (<18.5)	9	4.5
Normal (18.5-24.99)	103	51.5
Overweight (25.0-29.99)	73	36.5
Obese (≥30.0)	15	7.5
Diet type		
Vegetarian	34	17.0
Mixed	166	83.0
Abdominal obesity		
Yes	119	59.5
No	81	40.5
Physical activity		
Yes	73	36.5
No	127	63.5
Family history of diabetes		
Yes	45	22.5
No	155	77.5

Table 3 presents the differences between doctors and nurses regarding socio-demographic information, personal data, and occupational characteristics. Factors such as history of other illnesses, night shifts, and work-related stress were found to be statistically significant ($p<0.05$).

Table 4 outlines the risk levels among doctors and nurses based on the IDRS risk score. Most doctors (41.7%) and nurses (50.6%) had a moderate risk score in the study. However, the differences were not statistically significant ($p>0.05$).

Table 3. Occupational characteristics among doctors and nurses (n=200)

Occupational characteristics		**Doctors (%)**	**Nurses (%)**	**Total (%)**	**p value**
		115 (57.5)	**85(42.5)**	**200(100.0)**	
Residence	Urban	81(61.8)	50(38.2)	131(100.0)	0.087
	Rural	34(49.3)	35(50.7)	69(100.0)	
History of other illness	Yes	45(58.4)	32(41.6)	77(100.0)	0.038
	No	70(56.9)	53(43.1)	123(100.0)	
Night shifts	Yes	95(54.6)	79(45.4)	174(100.0)	0.031
	No	20(76.9)	6(23.1)	26(100.0)	
Working duration (years)	<6	8(80.0)	2(20.0)	10(100.0)	0.012
	6-10	86(61.8)	53(38.2)	139(100.0)	
	>10	21(41.2)	30(58.8)	51(100.0)	
Work-related stress	Yes	83(58.8)	58(41.2)	141(100.0)	0.54
	No	32(54.2)	27(45.8)	59(100.0)	

Table 4. IDRS Category score comparison among doctors and nurses (n=200)

IDRS Category	**Doctors (%)**	**Nurses (%)**	**Total (%)**	**p value**
Low (<30)	42 (36.5)	25 (29.4)	73 (36.5)	0.43
Moderate (30-50)	48 (41.7)	43 (50.6)	85 (42.5)	
High (>60)	25 (21.8)	17 (20.0)	43 (21.5)	

Discussion

The current study aimed to evaluate the diabetes risk among healthcare professionals working in a tertiary care hospital in Puducherry. The results indicated that most participants had a normal BMI (51.5%), followed by overweight individuals (36.5%) and those classified as obese (7.5%). Similarly, Kumar et al. [2018] [10] study found that the majority of participants were of normal weight (73.0%), with overweight individuals comprising 16.0%.

In this present study, 77.5% of participants reported having no family history of diabetes, while 22.5% did have such a history whereas Vidya et al. study [11] observed that 64.4% of participants lacked a family history of diabetes. Family history is a recognized risk factor for developing type 2 diabetes mellitus (DM), making it a valuable tool for identifying individuals at risk for the condition. In the present study, only 36.5% of participants reported engaging in physical activity, whereas Singh et al. [12] study found that around 55.2% of their participants had done moderate to vigorous physical activity.

In the present study, socio-demographic profile and occupational characteristics were compared among doctors and nurses. Factors such as history of other illnesses, night shifts, and work stress were found to be statistically significant ($p<0.05$). Similarly, Kumar et al. [10] study compared socio-demographic and personal data among Class 1 and Class 2 workers in a tertiary care hospital, where age, gender, residence, history of other illnesses, night shifts, and work duration were not statistically significant.

In this study, the prevalence of moderate risk was observed in 42.5% of participants, which is higher compared to a study conducted by Ranadip et al. [13]. In the present study, 21.5% of participants were classified as high risk, which was lower than the 31.0% reported in the Kolkata study. The discrepancy in findings may be attributed to the fact that the Kolkata study focused on the general population rather than healthcare professionals. Additionally, a study by Brinda et al. [14] found the distribution of low, moderate, and high-risk IDRS scores to be 26.0%, 49.0%, and 26.0%, respectively, whereas in our study, the figures were 36.5%, 42.5%, and 21.5%.

Conclusion

The present study presents a simplified Indian Diabetes Risk Score (IDRS) aimed at identifying unknown diabetic people in India. The IDRS provides a cost-effective method for diabetes screening by utilizing simple, safe, and inexpensive approaches. It promotes targeted screening instead of universal screening. The prevalence of moderate risk was found to be 42.5% and 21.5% respectively in Doctors and Nurses, which raises significant concern. Therefore, there is a need for implementing diabetes education and stress prevention programs tailored to the hospital's working population.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

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ORIGINAL ARTICLE

Neonatal Platelet Parameters as Early Markers for Diagnosis of Neonatal Sepsis

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Abstract

Background: Sepsis in the newborn population is one of the major cause of mortality and morbidity globally. Clinical symptoms and signs give clue for diagnosis of neonatal infection along with various diagnostics methods. This study aims to evaluate neonatal platelet parameters as early and inexpensive tool for diagnosing neonatal sepsis. **Methods**: This was a retrospective study, where 60 neonates with symptoms and signs of sepsis were enrolled and equally distributed into group 1 as neonates whose blood culture was sterile and septic screen was negative and group 2 as the ones with blood culture positive bacteremia. In enrolled neonates with suspected sepsis, before starting antibiotics, septic screen, platelets parameters were noted and MPV/TPC ratio was calculated. Clinical characteristics like need for vasopressor, need of ventilation and duration of NICU stay along with final outcome during hospitalisation were also noted. **Results:** The culture proven sepsis group had total platelet count significantly on lower side of normal (1.94 ± 0.70) and high MPV/TPC ratio (4.91 ± 2.14) along with increased need for vasopressor, ventilation and prolonged stay in NICU (*P*-value of 0.001). The cut off value ≥5.032 of MPV/TPC ratio had specificity of 96.67%, PPV of 92.31%, sensitivity of 40%, NPV of 61.7% and diagnostic accuracy of 68.33%. **Conclusion**: This study concludes that the investigative utility of MPV/TPC surpasses that of TPC or MPV alone in offering enhanced accuracy in early diagnosis of neonatal sepsis.

Keywords: Neonatal sepsis, neonatal platelet parameters, thrombocytopenia, MPV, MPV/TPC ratio

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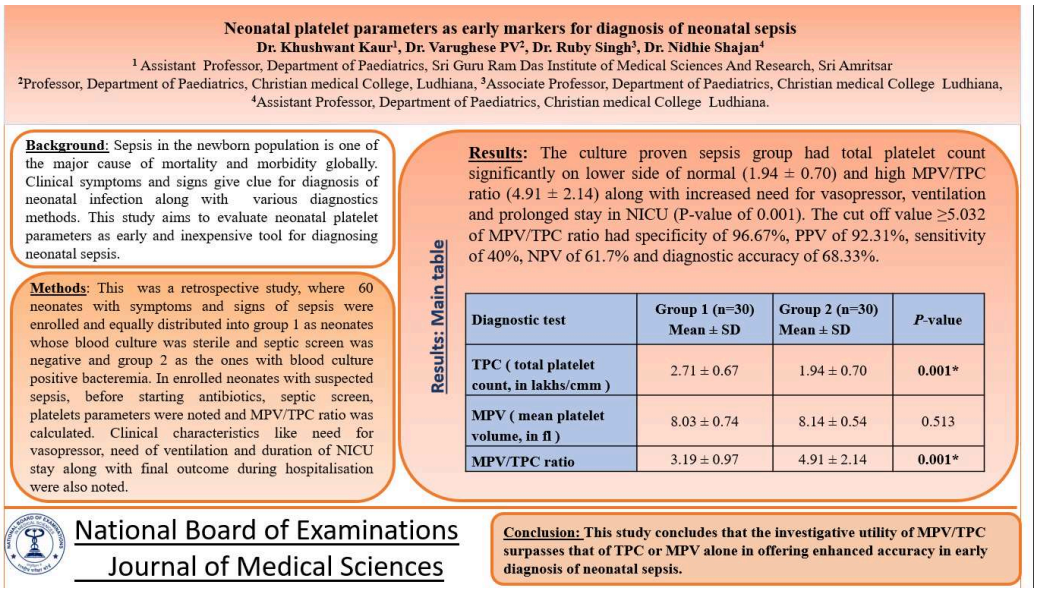
Graphical Abstract



Introduction

Sepsis neonatorum is one of the major causes of morbidity and mortality globally, more in India and in other developing countries. As per the National Family Health Survey 2019-2021 (NFHS-5), the current neonatal mortality rate (NMR) is 24.9 per 1000 live births [1]. The Delhi Neonatal Infection Study (DeNIS) collaboration reported the incidence of 6.2% in culture-positive sepsis and 14.3% in total (culture-positive or culture-negative) sepsis among all NICU admissions [2].

Symptoms and signs like lethargy, poor feeding, vomiting, skin pustules, diarrhoea, dehydration, umbilical discharge, fever, apnoea, hypothermia, tachypnoea, grunting, apnea, bradycardia, tachycardia, cyanosis, retractions, hypothermia, hypoglycemia, mottling, shock, abdominal distension, feed intolerance, seizures and sclerema may harbour reservations about early onset sepsis (EOS). As these mentioned findings are not specific for EOS, non infective causes may also present in a similar manner [3].

Neonatal sepsis is a serious, invasive and life threatening infection requiring expeditious therapy. In this condition, pathogens (viral, bacterial or fungal) enter the blood stream and lead to production of various toxins that further evoke a systemic inflammatory response (SIR) [4]. This leads to endothelial cell damage causing adhesion and aggregation of platelets. These toxins or pathogens can binds to platelets directly and then cause aggregation and dispatch of platelets from the circulation [5]. As a result there is destructive thrombocytopenia as platelets are rapidly expedited from the circulation. This prompts the production and release of newer platelets of variable sizes into the circulation.

The platelets when activated, release various inflammatory mediators and cytokines, that regulate inflammation and immune response in the body [6,7]. The cytokines like tissue factors when released in circulation act on coagulation system leading to over-activation and serious complications such as hypoxia followed by ischemia and disseminated intravascular coagulation (DIC) which can finally result in multiple organ dysfunction syndrome {MODS}[8,9].

The mean platelet volume (MPV) is considered a marker of platelet size, function reactivity and average volume of individual platelets [10]. An elevated MPV denotes the activity of the platelets, which can augment the early thrombus formation, followed by aggregation, adhesion and increased risk of severe complications, multiple organ dysfunction syndrome and death [11].

For diagnosing neonatal sepsis, detailed history for signs and symptoms, clinical examination, conventional diagnostic methods (isolation of pathogens from body fluids by cultures) and other diagnostic tests (including CRP, micro-ESR, WBC count, Absolute neutrophil count and IT ratio) are the mainstream methods [11].

Although it is time consuming but still blood culture is the gold standard method for diagnosis of infection in the body. Other limitation is positive blood cultures seen in limited number of cases only [12].

Since there is no ideal test or battery of tests that will help in definite diagnosis of sepsis hence it is imperative to identify a diagnostic test which is feasible, reliable and early, at the same time cost effective with acceptable sensitivity and specificity.

Several studies have been done on the functionality of platelet parameters in neonatal sepsis and have shown promising results [4,13-16]. These platelet parameters {total platelet count (TPC), mean platelet volume (MPV)} can be easily measured by rapid and cost effective routine blood count analyzer. MPV/TPC ratio is another promising platelet parameter that increases in platelet activation.

This study aims to find out the utility of neonatal total platelet count (TPC), mean platelet volume (MPV) and MPV/TPC ratio as an early and economical tool for diagnosing neonatal sepsis.

Material and Methods

This was a single Centre Retrospective descriptive study conducted in the Neonatology unit of a tertiary care hospital in North Western India. After institutional ethics committee clearance (IECBMHR/202401-006), 60 neonates of gestational age ≥34 completed weeks, admitted from January 1st 2022 to December 31st 2023 with suspected sepsis were included in study. Neonates with Major congenital anomalies, initiation of antibiotics prior to sending septic screen, incomplete records and

those born to mothers with immune thrombocytopenia (ITP) were excluded from the study. All the study participants enrolled were categorised into two groups. Group 1 included neonates with sterile/negative blood culture growth, negative sepsis screen and group 2 included neonates who had blood culture positive for sepsis. The patient records were retrieved from the medical records department. Data such as gestational age, birth weight, mode of delivery, gender, neonatal clinical characteristics during hospitalization like need of vasopressor, need of ventilation and duration of NICU stay along with final outcome were recorded. Neonatal septic screen {complete blood count (CBC), C-reactive protein (CRP) and blood culture as per institutional protocol} sent before starting antibiotics was also recorded.

For CBC, machine used was Beckman Coulter DxH800 which is based on the Coulter principle and Impedence method. Different organisms were isolated by Bactec blood culture.

All neonatal platelet parameters in CBC were noted and MPV/TPC ratio was calculated. The interpretation of neonatal MPV/TPC ratio was made easier by calculating it as "MPV(fl)/TPC (in lakhs/cmm)".

Statistical analysis

Results of both the groups were compared by standard statistical method. The data was analyzed using IBM SPSS software (ver. 26.0). The normality of the data was examined with the Kolmogorov–Smirnov test. Chi square test was conducted to compare categorical variables. The independent t-test was used to compare various platelet parameters of group 1 and 2. The maximum product of the sensitivity and specificity from the ROC analysis was used to determine the cut-off values. ANOVA has been used to compare the outcomes of various platelet parameters (TPC, MPV and MPV/TPC ratio) in case of expired neonates. Quantitative data was reported as mean ± standard deviation. Categorical data was presented as frequency (percentage). *P* value of less than 0.05 was considered statistically significant.

Results

This study was a retrospective cohort that included 60 neonates with signs and symptoms of sepsis. All the neonates enrolled were categorised into two groups. Group 1 included neonates with sterile blood culture, negative sepsis screen and group 2 included neonates with blood culture-positive sepsis.

The study groups were homogenous with respect to demographic profile in terms of gender, gestation, birth weight, mode of delivery, duration of rupture of membranes and presence of meconium stained liquor. No statistically significant difference was noted in distribution of these variables (*P*-value ≥.05). The details are mentioned in Table 1 below.

Table 1. Details of the demographic profile of study population

Demographic Details		Total n=60	Group 1 (Sterile blood Culture, Negative Sepsis Screen) n=30 N (%)	Group 2 (Blood Culture Positive Sepsis) n=30 N (%)	*P*-value
Gender	Males	31	16 (53.33)	15 (50)	0.796
	Females	29	14 (46.67)	15 (50)	
Gestation (in completed weeks)	34-37	26	16 (53.3)	10 (33.33)	0.177
	>37	34	14 (46.67)	20 (66.67)	
Birth Weight (in kg)	<1.5	3	0	3 (10)	0.168
	1.5-2.5	30	17 (56.67)	13 (43.33)	
	>2.5	27	13 (43.33)	14 (46.67)	
Mode Of Delivery	NVD	10	5 (16.67)	5 (16.67)	0.600
	LSCS	49	25 (83.33)	24 (80)	
	ABD	1	0	1 (3.33)	
Duration Of Rupture Of Membranes	I/O	41	19 (63.33)	22 (73.33)	0.227
	<24hrs	13	6 (20)	7 (23.33)	
	>24hrs	6	5 (16.67)	1 (3.33)	
Meconium Stained Liqour	Yes	25	12 (40)	13 (43.33)	0.793
	No	35	18 (60)	17 (56.67)	

A significant difference was observed between the two groups in terms of increased need for vasopressor and ventilation, prolonged stay in NICU and amplified mortality in blood culture positive sepsis group. Among the

neonates who had blood culture positive sepsis, 63.33% required vasopressor, 73.33% required ventilation, all were admitted in NICU for more than 72 hours and 20% had expired (*P*-value = 0.001). The details are mentioned in Table 2.

Table 2. Clinical characteristics of neonates during hospitalization

Clinical Characteristics During Hospitalisation		Total n=60	Group 1 n=30 N (%)	Group 2 n=30 N (%)	*P* – value
Requiring Vasopressor	No	41	30 (100)	11 (36.67)	0.001
	Yes	19	0	19 (63.33)	
Requiring Ventilation	No	38	30 (100)	8 (26.67)	0.001
	Yes	22	0	22 (73.33)	
Duration Of NICU Stay	<48 Hr	4	4 (13.33)	0	0.001
	48-72 Hr	11	11 (36.67)	0	
	>72 Hr	45	15 (50)	30 (100)	
Outcome	Discharge	42	28 (93.33)	14 (46.67)	0.001
	Dama	12	2 (6.67)	10 (33.33)	
	Expired	6	0	6 (20)	

Among 30 blood culture positive sepsis, 66.67% were gram negative sepsis {E.coli (30%), Acinetobacter (30%), Enterobacter (30%), Burkholderia (5%), Klebsiella (5%)}, 23.33% had gram positive sepsis {MRCONS (42.86%), CONS (42.86%), MRSA (14.28%)} and 10% had fungal sepsis {Candida (66.67%), Candida NA (33.3%)}. Among 6 blood culture positive sepsis neonates who expired 50% had gram negative sepsis {E.coli, Acinetobacter, Klebsiella (33.33% each)}, 33.33% had gram positive sepsis {CONS, MRSA (50% each)} and 16.67 % had fungal sepsis (Candida).

As shown in the Table 3, there was no statistically significant difference between two groups with respect to haemoglobin levels, total leucocyte count, percentage of Neutrophil, Lymphocyte, Monocyte and Eosinophil (*P*-value ≥0.05). There is significant difference in the mean of TPC and MPV/TPC ratio between the

two groups. The blood culture proven sepsis group had significantly lower platelet counts (1.94 ± 0.70) and higher MPV/TPC ratio (4.91 ± 2.14) than group 1.

Table 3. Comparison of haematological parameters of CBC between group 1 and group 2.

Diagnostic test	Group 1 (n=30) Mean ± SD	Group 2 (n=30) Mean ± SD	*P*-value
Hemoglobin (g/dl)	17.28 ± 2.32	17.26 ± 2.62	0.975
TLC (total leucocyte count, cells/cmm)	14950.0 ± 4759.15	14273.0 ± 5.88.79	0.597
Neutrophil (%)	60.50 ± 13.1	67.1 ±13.26	0.057
Lymphocyte (%)	31.80 ±11.7	27.47 ±11.33	0.15
Monocyte (%)	2.73 ± 1.62	2.27 ± 1.76	0.289
Eosinophil (%)	3.53 ±4.71	1.43 ±1.59	0.024
TPC (total platelet count, in lakhs/cmm)	2.71 ± 0.67	1.94 ± 0.70	0.001
MPV (mean platelet volume, in fl)	8.03 ± 0.74	8.14 ± 0.54	0.513
MPV/TPC ratio	3.19 ± 0.97	4.91 ± 2.14	0.001

The receiver operator curve characteristics (ROC) analysis for comparing the accuracy of various parameters of the platelets for neonatal sepsis is shown in Figure 1 and Table 4. The area under the curve for total platelet count (TPC), mean platelet volume (MPV) and MPV/TPC ratio was 0.784, 0.573 and 0.764 respectively. There difference in the mean ± SD of TPC (1.47 ± 0.68) and MPV/TPC ratio (6.61 ± 2.66) of expired neonates who had blood culture positive sepsis was significant.

Table 4. ROC analysis of platelet parameters for neonatal sepsis.

Diagnostic test	AUC (95% CI)	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic Accuracy (%)	*P*-value
TPC (Lakhs/cmm)	0.784 (0.672, 0.897	≤1.5	36.67	96.67	91.67	60.42	66.67	0.001
MPV(fL)	0.573 (0.425, 0.721)	≥7.850	63.33	56.67	28.89	62.22	68.33	0.333
MPV/TPC ratio	0.764 (0.647, 0.882)	≥5.032	40	96.67	92.31	61.7	68.33	0.001

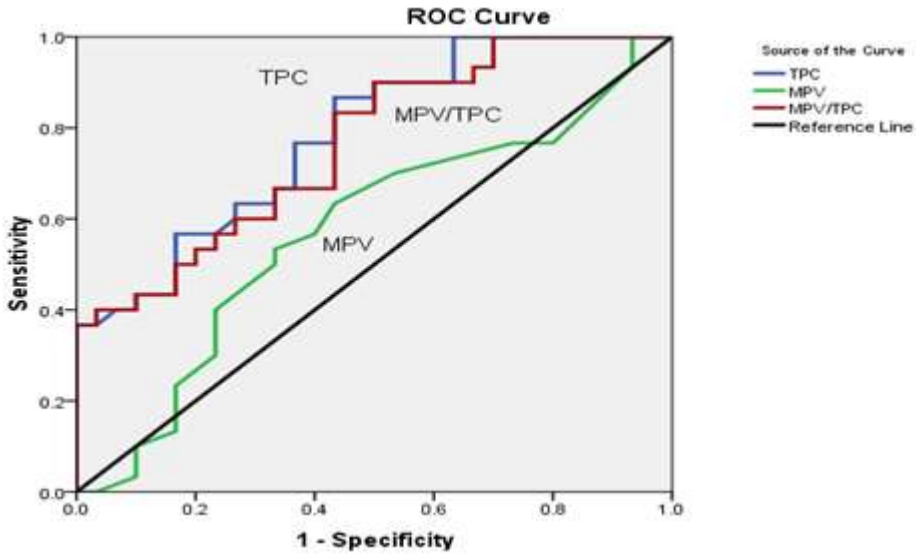


Figure 1. ROC curve analysis of TPC, MPV and MPV/TPC ratio for neonatal sepsis.

Discussion

Sepsis neonatorum being a fatal infection, remains a top reason of morbidity and mortality in newborns. Timely detection and management is pivotal to prevent consequences associated with bacteremia in newborns and improve impacts yet diagnosing it poses a big challenge. In our study 66.67% of newborns had blood culture positive for gram negative organisms, 23.33% had blood culture positive for gram positive organisms and 10% had fungal sepsis. Profile of bacteria, similar to our study, have been reported in various other studies [15,17,18].

Numerous studies have shown variable results for various platelet variables including TPC, MPV [4,10,11,13,15,16], platelet distribution width {PDW}[13,16,19,24] and platelet large cell ratio {P-LCR} [24].

Platelet count unfolds as a pivotal parameter for infection in newborns, often manifesting with a lower platelet count in severe cases. Our study showed that 91.67% of neonates who had culture positive bacteremia, had total platelet count below 1.5Lakhs/cmm. Our findings were comparable with the study done by Choudhary [19] where the incidence of thrombocytopenia was noted among 81.12% of the septicemic neonates. A study by Choudhary [16] found 64.7% neonates with culture proven neonatal septicemia had thrombocytopenia. The TPC cut off scale of 1.5lakh/cmm was further validated by our study, showing that among 12 neonates with this threshold, 91.67% neonates had culture positive bacteremia which was statistically significant (*P*-value 0.0001). There are various other studies that have affirmed thrombocytopenia as an important indicator of neonatal infection [14,20,21,22].

Mean platelet volume (MPV) is a measure of average size of platelets in blood which increases during platelet activation. In our study, the cut off value of MPV ≥7.850fl revealed a diagnostic accuracy of 68.33% but was found to be statistically insignificant (*P*-value ≥0.05). However out of 30 neonates with bacteremia, 63.33% had MPV values above the cut off value. Findings similar to our study were observed in a study by Karne [15] where MPV was increased in neonates with proven sepsis but did not show any relation between sepsis and MPV. Choudhary [19], Panda [23] and Bagchi [24] had higher MPV cut off values >10.8 fl, ≥9 fl and >10.5fl respectively {(*P*-value <0.0001)} as compared to our study. The sensitivity (63.33%) in our study was comparable to that reported by Panda [23] (63.4%) inferring that upper value of MPV may also occur in other systemic inflammatory conditions.

The MPV/TPC ratio has been studied in pneumonia and bacterial infection to identify platelet dysfunction, activation and consumption indicative of sepsis and inflammation in the body. In our study, a high MPV/TPC ratio (4.91 ± 2.14) was noted in neonates with bacteremia and those who had expired (6.61 ± 2.66) with significant *P*-value. At cut off value ≥5.032, MPV/TPC ratio had good specificity of 96.67%, positive predictive value (PPV) of 92.31%, sensitivity of 40%, negative predictive value (NPV) of 61.7% and diagnostic accuracy of 68.3%. Panda et al. [23] revealed high specificity (96.2 %), PPV (90.9%) at cut off value of ≥7.2 and Bagchi [24] reported similar observations of higher specificity (95.6%) and high PPV (90.2%) at cut off value ≥7.2 which further reinforces the findings in our study. Oh GH et al in their study done on adult population with blood culture proven bacteremia, stated that MPV/TPC ratio value exalted than cut off of 3.71 at admission was considerably associated with mortality risk (*P*-value = 0.001) [11]. Djordjevic et al. in his study done on critically ill patients, reported that

amongst all platelet parameters like platelet count, MPV and MPV/TPC ratio, ratio offered no advantage over other two parameters [21].

In the ROC analysis of platelet parameters of our study, area under the curve (AUC) for MPV/TPC ratio was **(**0.764) better than MPV. We observed that MPV/TPC ratio had better specificity, PPV, sensitivity, NPV and diagnostic accuracy than MPV. Although AUC for TPC was (0.784) more than MPV/TPC ratio (0.764) but MPV/TPC ratio had identical specificity but higher PPV, NPV, sensitivity and diagnostic accuracy than TPC.

Regarding the MPV/TPC ratio, the cut of value of ≥5.032 was further solidified by the fact that the 13 neonates who had value above the cut off, 92.3% neonates had blood culture-positive septicemia which was statistically significant (*P*-value 0.001). Our study exemplify excellent specificity (96.67%) and high positive predictive value (92.31%) for MPV/TPC ratio, shore it up to be superior upcoming diagnostic marker in neonatal sepsis.

Conclusion

From the current study, it was concluded that amongst platelet parameters, low TPC and a higher MPV/TPC ratio at the designated cut off values, fulfil the role as important marker for diagnosis of infection in neonates and should be utilized as early marker for diagnosis of sepsis neonatorum. These parameters when combined with detailed history, complete clinical examination and CRP can be used as early, ubiquitous and cost effective markers for diagnosis of sepsis neonatorum. The diagnostic performance of MPV/TPC is preeminent to MPV or TPC alone in early diagnosis of sepsis in neonatal population.

Limitation

It was a single centre retrospective study with a small sample size. Hence a prospective, multicentric study with large sample size will add strength to future studies.

Statements and Declarations

Conflicts of interest

The authors declares that they do not have conflict of interest.

Funding

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ORIGINAL ARTICLE

Case Fatality Rate and Neurological Morbidity in Neonates with Sepsis in a Tertiary Care Neonatal Intensive Care Unit in a Developing Country

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Abstract

Background: The case fatality rate (CFR) for neonatal sepsis and its determinants vary from unit to unit. Sepsis may have a detrimental impact on neurodevelopment too. **Materials and Methods:** It is a descriptive observational study of neonates with culture-proven sepsis to determine the CFR, prevalence, predictors of mortality, and neurological morbidity. A neurological examination (Hammersmith neonatal neurological examination) was done at discharge. **Results**: The prevalence and CFR of proven sepsis were 24.5% (314/1282) and 24%, respectively. The greatest CFR was seen in neonates with Acinetobacter sepsis. On logistic regression, decreased movements (OR-5.48; 95% CI-2.17–13.83), convulsions at admission (OR-2.42; 95% CI-1.19–4.92), and Acinetobacter in blood culture (OR-1.42; 95% CI-0.65-3.10) were the significant predictors of mortality. Twenty-four (11%) neonates had abnormal neurological examination at discharge and convulsions at admission (OR 3.12; 95% CI 1.04–9.35), and Acinetobacter in blood culture (OR 4.87; 95% CI 1.51–5.66) were the significant predictors of neurological morbidity. **Conclusion:** A quarter of neonates with sepsis die, and more than a tenth have neurological morbidity.

Keywords: Culture proven neonatal sepsis; case fatality rates; neurological morbidity; developing country

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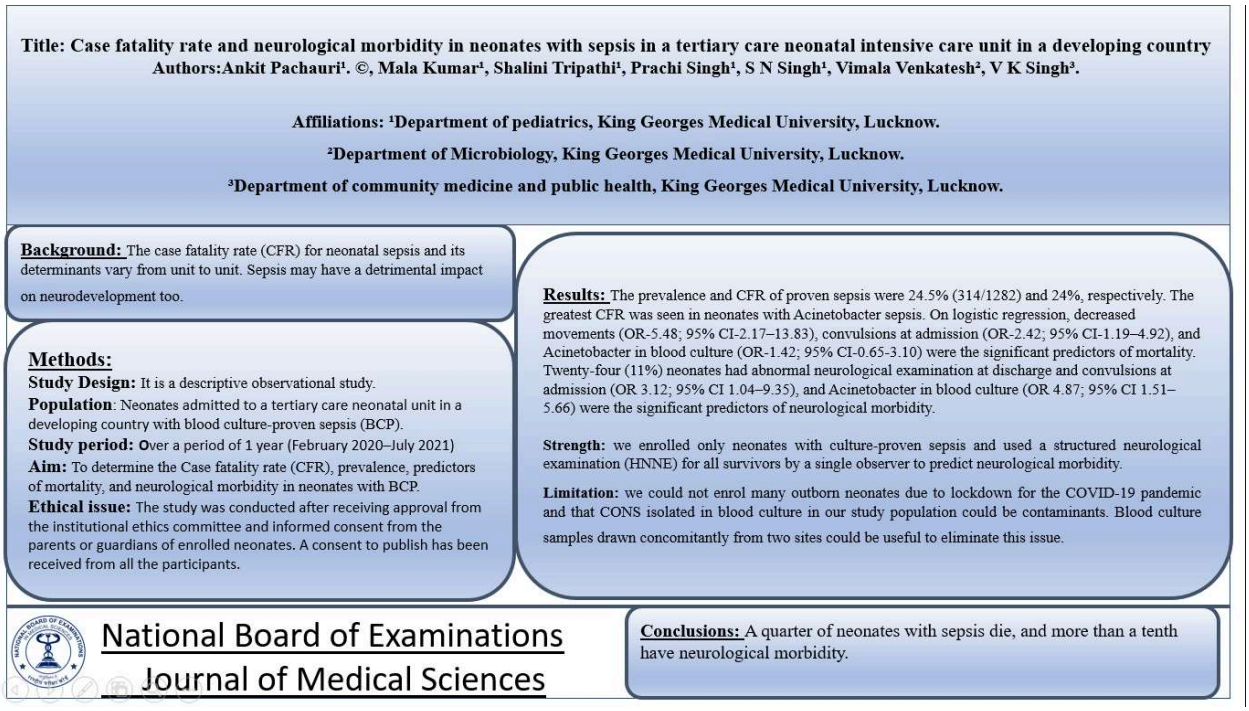
Graphical Abstract



Background

Sepsis is the third-most common cause of neonatal death globally [1]. Out of 5.2 million under-5-year-old deaths from preventable and treatable causes, neonates accounted for 2.4 million deaths [2].

India has made a significant contribution to the reduction of global newborn mortality, with its share of the global newborn mortality burden coming down to less than a quarter today from one third of total newborn deaths in 1990 [3,4]. Still, the burden of neonatal sepsis is huge in our country. Nearly one-fifth of neonates with sepsis die in the hospital, which rises to 50% for those with culture-proven sepsis [5].

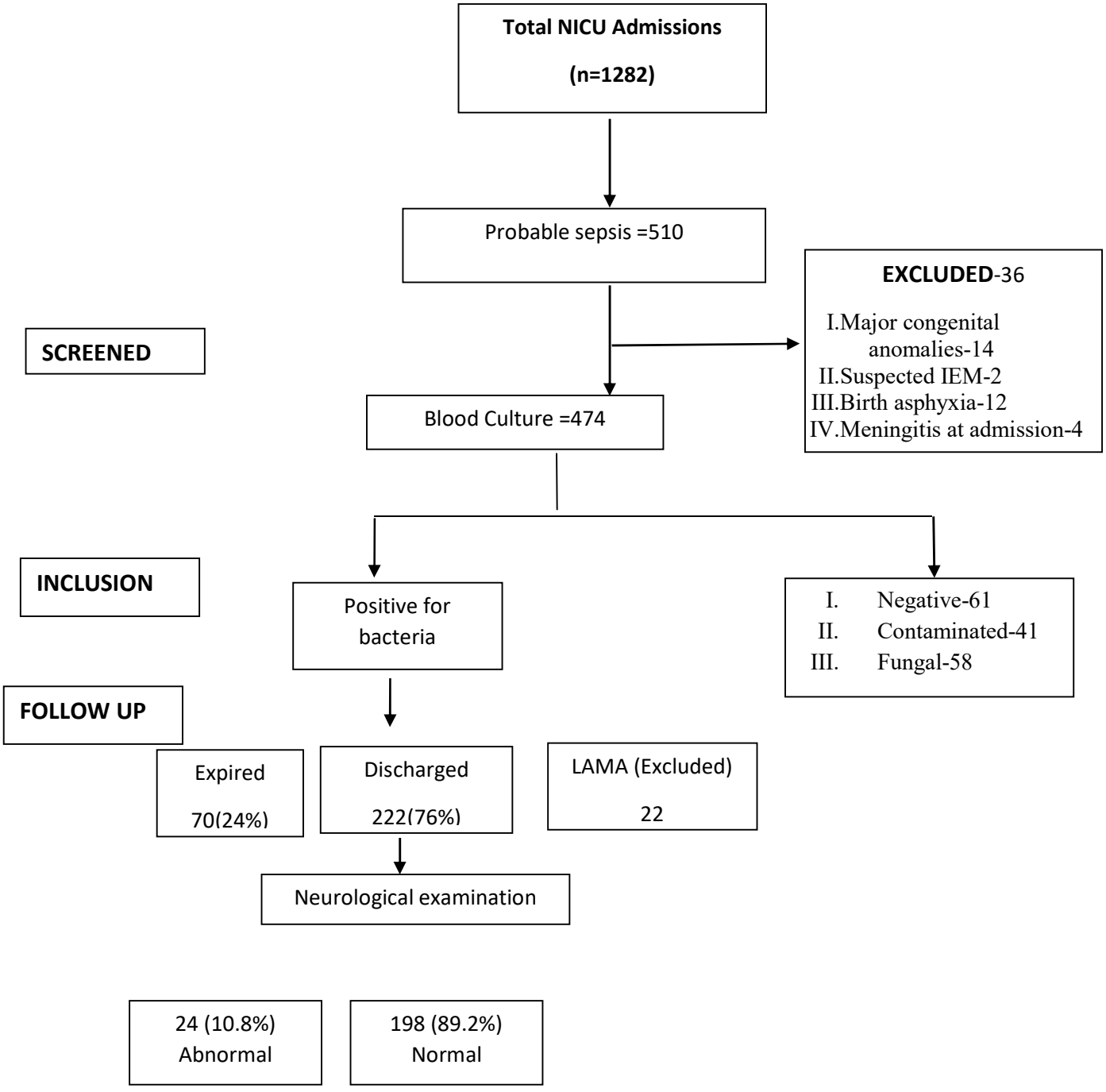
Case fatality rates for neonatal sepsis are different in different countries and even in different units of the same country. These rates depend on a number of factors, like level of care, human resources, and infrastructure. It also depends on the type of patients being admitted to the unit, whether inborn or outborn, term or preterm, and demographic characteristics like socioeconomic status. Therefore, it is essential to know the case fatality rate (CFR) in a unit, keeping in mind the determinants of mortality and morbidity in a unit.

Sepsis may have a detrimental impact on the neurodevelopment of neonates. Bacteremia-related neurological complications (BNC) are quite prevalent. The major BNCs consist of seizures, hydrocephalus, encephalomalacia, cerebral infarction, subdural empyema, ventriculitis, and abscess [6]. Since not only neonates with clinical signs of CNS involvement and proven meningitis have neurological sequelae, it becomes important to evaluate all neonates with sepsis for neurological outcome. We have conducted this study to

determine the CFR, neurological outcome of neonates with blood culture-positive (BCP) sepsis, and common determinants of mortality and morbidity in our unit.

Methods

Study Flow:



Study design

It was a prospective observational study conducted on neonates with sepsis admitted to a tertiary care neonatal unit in a developing country over a period of 1 year (February 2020–July 2021). Consecutive neonates with blood culture-positive sepsis (BCP) were enrolled. A neurological examination (NE) by Hammersmith Neonatal Neurological Examination (HNNE) was done at discharge for those who survived sepsis.

Population

Inclusion criteria: Neonates admitted in NICU with probable sepsis and growing a bacterial pathogen in blood culture.

Exclusion criteria: Major congenital malformations, suspected inborn errors of metabolism, not giving consent, meningitis on admission, birth asphyxia.

The primary objective of the study was to determine the CFR for neonates with sepsis. Secondary objectives were to study the prevalence, predictors of mortality, and neurological morbidity of these neonates. Those with a positive blood culture were included in the study. Neonates with major congenital malformations, suspected inborn errors of metabolism, birth asphyxia, meningitis at admission, or leaving against medical advice were excluded. Their baseline characteristics were noted from their records, and they were followed up prospectively till they were discharged, died, or left the hospital against medical advice. Neonates were managed according to the standard protocols of the unit. Relevant investigations were done, and the neonates were examined at the time of discharge or term equivalent age for any neurological morbidity by HNNE. The expired or discharged neonates and those with abnormal or normal NE were compared for the predictors.

Hammersmith Neonatal Neurological Examination (HNNE): A short HNNE proforma was used to do neurological examinations of neonates with sepsis at discharge. It consists of 12 items, of which 11 are set out in 3 columns, with 2 lateral columns reported as warning signs. The last item includes five abnormal neurological signs to be scored as yes or no. The babies in whom neurological findings were falling in the central grey column were within the reference range (90%) and taken as normal, and those falling in any of the warning sign lateral columns were labelled abnormal. In addition to this, the last row “abnormal signs” has to be circled as Yes or No for each sign [7].

Statistics

Sample size: Taking a mortality rate of 25%, as the developing countries have 2.7–50% mortality in neonates (8, 9, 10, 11) and the western world has a mortality rate of 4–18% (8, 9, 12) with sepsis, a sample size of 300 was calculated using the formula:

$= \{Z_{(\alpha/2)}\}^2 pq/e^2$
$= (1.96)^2\ (0.25)\ (0.75)\ 0.5x0.5 = 288 \sim 300$
Z = 1.96 for 95%
p= proportion of neonates dying (mortality) - 25%
q = (1-p)
e = allowable error- 5%

Statistical Analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD and median. Odds ratios with 95% confidence intervals were calculated for selected variables as needed. Quantitative variables were compared using an unpaired t test between the two groups. Qualitative variables were compared using the chi-square or Fischer's exact test as appropriate. A p-value of <0.05 was considered statistically significant. The logistic regression analysis was done to find the independent factors associated with CFR and abnormal NE at discharge. The data was entered in an MS Excel spreadsheet, and analysis was done using the Statistical Package for Social Sciences (SPSS) Version 24.0.

Results

During the study period, 1282 neonates were admitted to our neonatal unit, of whom 314 had blood culture-positive sepsis and were enrolled. Of 314 enrolled neonates, 70 (24%) expired, 222 (76%) were discharged, and 22 were left against medical advice (LAMA). Neonates who went to LAMA were excluded from the study. So, the study comprised 292 neonates with blood culture-positive sepsis.

Table 1 shows a comparison of the baseline characteristics of expired and discharged neonates. The two groups were different for birth weight (p<0.001), gestational age (<0.001), and type of delivery (0.005).

Table 1. Baseline characteristics of expired and discharged neonates with sepsis

Baseline characteristics		**Expired neonates (n=70) No (%)**	**Discharged neonates (n=222) No (%)**	**p-value**
Birth weight	< 1000 g	8 (11.4%)	8 (3.6%)	**<0.001**
	1000-1499 g	24 (34.3%)	27 (12.1%)	
	1500-2499 g	20 (28.6%)	105 (47.3%)	
	>=2500 g	18 (25.7%)	82 (37%)	
Gestational Age	Preterm	46 (65.7%)	97 (43.7%)	**0.001**
	Term	24 (34.3%)	125 (56.3%)	
Onset of sepsis	EOS	57 (81.4%)	194 (87.4%)	0.211
	LOS	13 (18.6%)	28 (12.6%)	

Sex	Female	27 (38.6%)	97 (43.7%)	0.450
	Male	43 (61.4%)	125 (56.3%)	
Type of delivery	Cesarian section (LSCS)	25 (35.7%)	126 (56.75%)	**0.005**
	NA	0 (0.0%)	2 (0.9%)	
	Vaginal	45 (64.3%)	94 (42.35%)	
Place of delivery	Inborn	43 (61.4%)	139 (62.6%)	0.859
	Outborn	27 (38.6%)	83 (37.4%)	

NA-Not applicable as destitute neonate; EOS- Early onset sepsis; LOS- Late onset sepsis.

Table 2 shows predictors of mortality based on univariate analysis. The predictors were CONS and Acinetobacter in blood culture, tachycardia (HR>160/min.), bradycardia (HR-<100/min), temp >37.5 deg C, temp <35.5 deg C, decreased cry, decreased movements, RR>60/min, apnea, grunting, Spo2<90%, capillary refill time >3sec, hypotension, mottling, sclerema, abdominal distension, vomiting, hypoglycemia, convulsion, bulging AF, infiltrates on chest x-ray (p value<0.05). Also, during hospital stays, neonates requiring ventilation >48 hours, convulsions requiring AED, meningitis, and shock requiring vasopressors were more likely to die (p values <0.001, 0.011, <0.001, and <0.001, respectively).

Table 2. Predictors of case fatality rate in neonates with sepsis

Predictors	**Expired neonates (n=70)**	**Discharged neonates (n=222)**	**p-value**
	No (%)	No (%)	
Tachycardia (>160/min)	47 (67.1%)	92 (41.4%)	**<0.001**
Bradycardia (<100/min)	44 (68.5%)	86 (38.7%)	**<0.001**
Temp > 37.5°C	29 (41.4%)	43 (19.4%)	**<0.001**
Temp < 35.5°C	40 (57.1%)	70 (31.5%)	**<0.001**
Decreased movements	64 (91.4%)	144 (64.8%)	**<0.001**
RR> 60/min	63 (90%)	175 (78.8%)	**0.036**
Apnoea	31 (44.3%)	57 (25.7%)	**0.003**

Grunting	47 (67.1%)	95 (42.8%)	**<0.001**
Mottling	32 (45.7%)	10 (45%)	**<0.001**
Sclerema	32 (45.7%)	6 (2.7%)	**<0.001**
Abdominal distension	47 (67.1%)	75 (33.8%)	**<0.001**
Vomiting	62 (88.6%)	129 (58.1%)	**<0.001**
Hypoglycemia	60 (85.7%)	115 (51.8%)	**<0.001**
Hyperglycemia	15 (21.4%)	44 (19.8%)	0.770
Convulsion	23 (32.8%)	39 (17.6%)	**0.006**
Bulging AF	19 (27.1%)	6 (2.7%)	**<0.001**
Shock requiring vasopressors	63 (90%)	69 (31.1%)	**<0.001**
Infiltrates on chest x-ray	59 (84.3%)	143 (64.4%)	**0.002**
Ventilation for>48hrs	53 (75.7%)	51 (22.9%)	**<0.001**
Meningitis on admission	27 (38.5%)	7 (3.2%)	**<0.001**
CONS	23 (16.1%)	120 (83.9%)	**0.002**
Acinetobacter spp.	22 (37.9%)	36 (62.1%)	**0.005**
K.pneumoniae	13 (35.1%)	24 (64.9%)	0.089
S.aureus	3 (15.8%)	16 (84.2%)	0.388

AED-antiepileptic drugs; RR >60/min- respiratory rate >60/minute; Temp- Temperature; CONS-coagulase negative staphylococcus

Table 3 shows the factors associated with mortality in logistic regression. They were decreased movement (OR-5.48; 95% CI-2.17–13.83), convulsions at admission (OR-2.42; 95% CI-1.19–4.92), and CONS in blood culture (OR-0.43; 95% CI-0.21-0.86).

Table 3. Logistic regression analysis for prediction of mortality in neonates with sepsis

Parameters	**B**	**SE**	**p-value**	**OR**	**95% C.I.for OR**	
					Lower	**Upper**
Temp > 37.5°C	0.57	0.37	0.117	1.78	0.87	3.65
Temp < 35.5°C	0.50	0.36	0.160	1.65	0.82	3.31
Decreased movement	1.70	0.47	**<.001**	5.48	2.17	13.83
RR>60/min	0.48	0.48	0.317	1.61	0.63	4.10

Convulsion	0.89	0.36	**0.014**	2.42	1.19	4.92
CONS	-0.84	0.36	**0.018**	0.43	0.21	0.86
Acinetobacter	0.35	0.40	0.377	1.42	0.65	3.10
Constant	-0.41	0.55	0.459	0.66		

B- beta coefficient; SE -standard error; OR- Odds ratio; C.I- confidence interval; RR >60/min-respiratory rate >60/minute; Temp- Temperature; CONS- coagulase negative staphylococcus.

Table 4 shows the factors associated with abnormal neurological examinations based on logistic regression. Convulsions at admission (0.042; 1.04–9.35) and Acinetobacter in blood culture (0.008; 1.52-15.66)

Table 4. Logistic regression analysis for prediction of abnormal neurological outcome in neonates with sepsis

Parameters	**B**	**SE**	**p-value**	**OR**	**95% C.I. for OR**	
					Lower	**Upper**
Temp > 37.5°C	1.11	0.57	0.054	3.03	0.98	9.33
Temp < 35.5°C	0.79	0.53	0.141	2.20	0.77	6.26
convulsion	1.14	0.56	**0.042**	3.12	1.04	9.35
CONS	-0.80	0.62	0.195	0.45	0.13	1.51
Acinetobacter	1.58	0.60	**0.008**	4.87	1.52	15.66
Constant	-0.74	0.87	0.393	0.48		

B- beta coefficient; SE -standard error; OR- Odds ratio; C.I- confidence interval; RR >60/min-respiratory rate >60/minute; Temp- Temperature; CONS- coagulase negative staphylococcus

Discussion

In our study, the fatality rate for neonatal sepsis was 24%. Decreased movements and convulsions at admission and Acinetobacter in blood culture were the significant predictors of mortality.

Studies done in other tertiary care centres have found similar rates. CFR in different countries in South Asia ranged from 19.1% to 64.7% [8], and that for Indian neonates was 34.4% [8].

In another study from six developing countries (India, Pakistan, Bangladesh, Bolivia, Ghana, and South Africa), a lower CFR for culture-positive and culture-negative sepsis was suspected at 7% and 7.5%, respectively, but the setting was community-acquired sepsis [9].

The prevalence of BCP sepsis in our NICU was 24.5%. It was less as compared to other studies, like one from Karnataka with a prevalence of 28.8% [11] and 45.1% from Bhopal [13]. The incidence of culture-positive sepsis per 1000 live births in India was 16% [8], while according to other studies, it was 14.5% in Delhi [5] and 10.5% in a study conducted in six countries [9].

In our analysis, EOS (86%) was more common than LOS (14%). The most frequent pathogens (CONS, Acinetobacter, and Klebsiella pneumoniae) for both EOS and LOS were comparable in our study. While late-onset sepsis was more prevalent, these data were comparable to those of Ballot ED et al. (2012) [12]. Acinetobacter was shown to be the most common (22%) organism causing newborn sepsis with a significant incidence of multidrug-resistant infections in the Delhi newborn infection study (DeNIS) consortium (2016) [5].

The clinical characteristics of neonates with sepsis at admission were similar in our study to those of several other studies. Vomiting, increased respiratory rate, and lethargy were the most common and were found more frequently than in other studies [14,15]. Fever, convulsions, and sclerema were found in fewer patients as compared to other studies.

Sepsis may have a neurological morbidity, so we did a neurological exam of neonates with sepsis at discharge in an effort to estimate the proportion of bacteremia-related neurological morbidity. We found that more than 10% of neonates had abnormal HNNE at discharge, and it was mainly in the form of a tone abnormality. These neonates were in our follow-up, and out of these, five patients had an MRI brain at 6 months of age, and all were abnormal. Two had encephalomalacia, one had a cerebral infarction, and two had features suggestive of hypoxic ischemic encephalopathy; three had abnormal BERA and two abnormal EEGs, one of which was suggestive of hypsarrhythmia.

In another study, developmental delay was reported in 23.4% of neonates with sepsis when followed up for 6 months [16]. Another observational cohort study found that bloodstream infection-associated complications were reported in 10.4% of the patients with BSI, neurological complications comprised 33.7%, and persistent sequelae were seen in 18.3% [17].

In our study, 50% of abnormal NE was associated with Acinetobacter sepsis. Predictors of abnormal neurological examination at discharge were Acinetobacter (p value <0.001) in blood culture and convulsions (p value 0.039), bulging AF (p value <0.001), and hypoglycemia (p value 0.048) at admission. Morbidities like neonates requiring ventilation for >48 hours and developing shock during hospital stays were significantly more associated with abnormal neurological examinations, with p values <0.001 and 0.012, respectively. On logistic regression, convulsions and Acinetobacter in blood culture were the significant predictors of abnormal neurological outcomes. The OR for Acinetobacter was 4.87, and for convulsion, the OR was 3.12.

Strength

We enrolled only neonates with culture-proven sepsis and used a structured

neurological examination (HNNE) for all survivors by a single observer to predict neurological morbidity.

Limitation

We could not enrol many outborn neonates due to lockdown for the COVID-19 pandemic and that CONS isolated in blood culture in our study population could be contaminants. Blood culture samples drawn concomitantly from two sites could be useful to eliminate this issue.

Conclusion

Neonatal sepsis accounted for a quarter of total neonates admitted to our unit. CONS, Acinetobacter, and Klebsiella pneumoniae were the most common organisms isolated. Predictors of mortality were decreased movement, convulsions at admission, and Acinetobacter in blood culture. More than a tenth of neonates with BCP had abnormal neurological morbidity, and predictors of this were convulsions at admission and Acinetobacter in blood culture.

Ethical Approval

The study was conducted after receiving approval from the institutional ethics committee and informed consent from the parents or guardians of enrolled neonates. A consent to publish has been received from all the participants. No monetary or personal benefits from commercial bodies were provided to anybody involved in the study. Confidentiality of the data was maintained.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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ORIGINAL ARTICLE

Comparative Study of Vitamin D Status in Late Preterm and Term Neonates with Sepsis and Healthy Neonates in a Tertiary Care Hospital in Northern India

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Abstract

Objective: Comparative study of vitamin D status in late preterm and term neonates with sepsis and healthy neonates in a tertiary care hospital in Northern India. **Methods:** In this hospital-based case control study conducted over 12 months, a total of 70 late preterm and term neonates were included, with 35 neonates each in the sepsis group and non-sepsis group. The difference between the mean vitamin D level of the neonates with sepsis and neonates without sepsis group was calculated. The association of VDD with neonatal sepsis was determined by multivariate logistic regression analysis. P value of 0.05 was considered statistically significant. **Results:** The study found that about 80% of neonates in the septic group and 52% of neonates in the non-septic group had vitamin D deficiency. The mean Cholecalciferol in the septic group (13.51 ng/ml ± 6.56 ng/ml) was significantly lower (p value 0.02) than in the non-septic group (24.47 n/ml ± 8.73 ng/ml). There was a positive correlation between degree of vitamin D deficiency (severe VDD and insufficiency) and sepsis ($p = 0.005$). Prolonged hospital stay and antibiotic treatment were observed in the septic group ($p < 0.001$) with significant mortality ($p < 0.001$). Logistic regression analysis showed that lower vitamin D levels, maternal hypertension, premature birth, and lower birth weight significantly increased the odds of sepsis, highlighting these as predictive factors for adverse outcomes. **Conclusion:** The study showed a significant association of neonatal sepsis with vitamin D. The study highlights extended hospital stays and increased mortality among septic neonates with vitamin D deficiency.

Keywords: Vitamin D; Sepsis; Late Preterm; Term; Hospital stay

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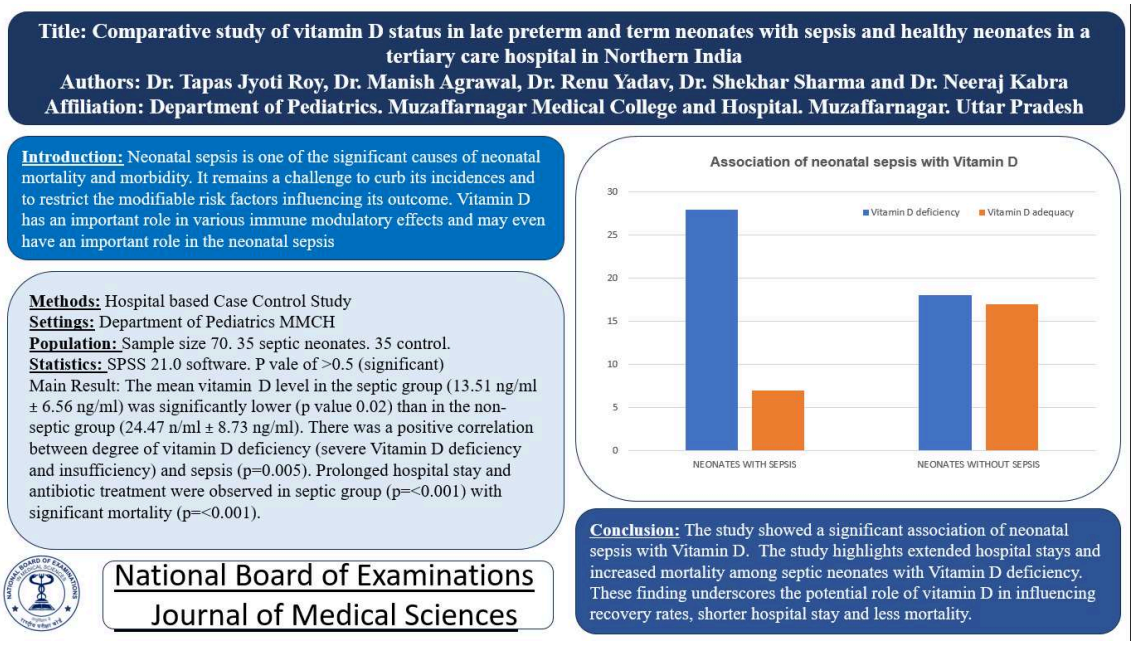
Graphical Abstract



Introduction

Mortality in newborn periods accounts for 47% of under-5 mortalities [1]. The neonatal mortality rate worldwide is 19 per thousand live births [2]. In India, neonatal mortality is higher, at 20 per 1000 live births, and it constitutes 62.5% of all under-5 deaths [3]. Neonatal sepsis accounts for about 25% of the total neonatal deaths [4]. Sepsis in newborns manifests with various clinical features of infection, with or without bacteremia, in the initial 4 weeks of life. It includes septicaemia, pneumonia, meningitis, UTI, osteomyelitis, and arthritis but excludes superficial infections [5]. Early-onset sepsis manifests within the first 3 days of a newborn's life [6]. It primarily results from infections transmitted while the baby passes through the genital tract of the mother during childbirth. Late-onset sepsis typically manifests itself after the initial 72 hours of a newborn's life and is often presumed to be the result of infections transmitted horizontally, predominantly through the hands of those providing care [6]. Management of sepsis in newborns is challenging due to its subtle and confusing clinical features, absence of definite and specific biomarkers, judicious requirement for starting empirical and high-cost antibiotics, and emergence of resistance to antibiotics. Thus, preventive approaches, including the identification of risk factors and various modifiable adjuvant therapies, have become areas of newer research interest in the battle against sepsis in newborns.

The function of vitamin D extends beyond its well-known roles in calcium and phosphorus metabolism affecting the skeletal system [7]; it has a role in certain systemic conditions like various autoimmune disorders, certain cancers, cardiac diseases, and metabolic syndromes. It exerts its immunological action mainly by binding with the vitamin D receptor on the cells of monocytes, macrophages, and neutrophils, leading to augmented chemotactic, phagocytic, and bactericidal

activities [8]. Low levels of vitamin D were seen in pregnant mothers and neonates worldwide [9]. The immune modulator role of vitamin D and the increasing global pandemic of vitamin D deficiency have stoked the speculation of a possible relation of VDD with sepsis in newborns [10].

The rationale for such a comparative study of the status of cholecalciferol in newborns with sepsis and healthy newborns in a tertiary care hospital in northern India stems from the fact that the identification and proper timely management of sepsis and VDD in such newborns may have a short-term as well as a long-term prognostication value.

Material and Methods

This hospital-based case control study was conducted from September 2022 to August 2023 in the Department of Paediatrics, Muzaffarnagar Medical College and Hospital, Muzaffarnagar, UP. A total of 70 late preterm and term neonates were included, with 35 neonates each in the sepsis group and non-sepsis group. Cases included all neonates over 34 weeks of gestational age with sepsis within days of life 28 who were admitted to the NICU. Cases also included those with probable sepsis, culture-positive sepsis, and clinical sepsis. Healthy newborns in the postnatal ward roomed in with mothers over 34 weeks of gestation without any sepsis were taken as control. Neonates with major congenital anomalies, receiving formula feed, starting on supplementation of vitamin D, or less than 34 weeks of gestation were excluded.

A written informed consent was obtained from parents or guardians before enrolment of each baby in the study. Demographic details of the mother and the newborn were collected. In a predesignated validated pro forma, all clinical findings and relevant investigations were documented. Gestational age was assessed by the LMP and the new Ballard score. Haemoglobin, TLC, C-Reactive Protein, ESR, I/T Ratio, ANC, and blood culture, which were noted.

A Practical Sepsis Screen

Components	Abnormal Value
Total leukocyte count	<5000/mm^3
Absolute neutrophil count	Low counts as per Manroe Chart[21] for term and Mouzinho's chart[22] for VLBW infants
Immature/ total neutrophil	>0.2
Micro-ESR	>15mm in 1st hour
C reactive protein (CRP)	>1mg/dL

Before initiating antimicrobial therapy, blood cultures were taken. Aseptic measures were taken before collecting blood culture samples. 1 ml of blood in 10 ml of broth for blood culture was collected. Colonies were examined after 24, 48, 72, and 120 hours.3 ml of blood collected under aseptic precautions was sent for routine examinations. CBC was done using a blood count analyser (Bachman Coulter). Serum Cholecalciferol assay was done in healthy newborns (control) within DOL 3 and in cases of newborns with culture-positive sepsis or with suspicion of sepsis done before the antibiotic was started. Serum cholecalciferol was assessed by an immunoassay system (detects concentration of vitamin D using an antibody as reagent) - Beckman Coulter Access 2 Immunoassay System. Cholecalciferol levels were assessed in ng/mL.Serum vitamin D levels less than 12 ng/ml indicated severe deficiency; insufficiency was 12 to 20 ng/ml, and 20 to 100 ng/ml indicated adequacy.

CRP levels were quantified using the immunoturbidimetric method. The detection limit for CRP was 1 mg/dl.

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS), version 21. Continuous variables have been represented as mean ± SD. Category variables have been displayed as frequencies and percentages. The independent sample t-test was used while comparing vitamin D levels in two groups. A chi-square test or Fisher's exact test was used to compare between two groups. The association of VDD with neonatal sepsis was determined by logistic regression analysis and expressed as an odds ratio. A P value <0.05 was considered statistically significant for this study.

Table 1. Maternal sociodemographic status

Variables	**Cases**	**Controls**	**p-Value**
Age (yrs)			
<20	7(20%)	2(6%)	**0.02**
20-30	18 (51%)	26 (74%)	
>30	10 (29%)	7 (20%)	
Education			
Illiterate	10 (29%)	2 (6%)	**0.04**
Primary	10 (29%)	8 (23%)	
Secondary	10 (29%)	15 (43%)	
Higher	5 (14%)	10 (29%)	
SES			
Lower	20 (57%)	8 (23%)	**0.003**
Middle	15 (43%)	27 (63%)	
Residence			
Urban	20 (57%)	30 (86%)	**0.03**
Rural	15 (43%)	5 (14%)	
Children			
1	10 (29%)	20 (57%)	**0.015**
>1	25 (71%)	15 (53%)	

Results and Discussion

Regarding socio-demographic characteristics of the mothers (Table 1), it was observed that there were a greater number of mothers aged less than 20 years, in the sepsis group (20% vs. 6%). In the control group, 74% of the mothers were in the 20-30 year group, compared to 50% in cases. It suggested that lower age at conception had a direct correlation (p = 0.02) with sepsis and VDD; this finding was similar to the study by Bitew et al. [11] which showed a higher proportion of women who bore children before the age of 20 had higher incidences of sepsis and VDD. Maternal education exhibits a notable distinction, with cases showing higher percentages of mothers with no education (29% vs. 6%, p = 0.04) and primary education (29% vs. 23%) compared to controls. In terms of socioeconomic status, statistically significant differences are observed between cases and controls, with sepsis cases being more predominant among lower socioeconomic groups. Notably, location of residence shows a significant disparity, with cases more likely to reside in

rural areas compared to controls (43% vs. 14%, p = 0.03), suggesting environmental or resource-based factors could influence health outcomes. Regarding the number of children in the household, there is a significant trend towards smaller households (single child) among controls, while neonates with sepsis belonged more to larger households. (p= 0.015). This suggests that with multiple children and with a decreased gap between 2 pregnancies, mothers may have poor nutritional status as well as low vitamin D levels, causing them to have children who are prone to VDD and sepsis. Odabasi et al. [12] study on sepsis also showed greater incidences of sepsis and VDD in rural, illiterate, and multiparous mother.

Table 2. Neonatal Baseline Characteristics

Variables	**Cases**	**Controls**	**p-Value**
Gestational Age (wks)	**36.77 ±1.26**	**36.60 ± 1.75**	
Late Preterm	15(42%)	16(45%)	0.8
Term	20 (48%)	19(55%)	
SGA	18 (51%)	9 (25%)	0.27
AGA	17 (49%)	26 (71%)	
Male	16 (49%)	17 (52%)	0.8
Female	19 (51%)	18 (48%)	
LSCS	21 (54%)	25 (71%)	0.3
VD	14 (46%)	10 (29%)	
Inborn	8 (23%)	33 (94%)	**<0.001**
Outborn	27 (77%)	2 (6%)	

Regarding baseline characteristics of neonates in the study group (Table 2), the mean gestational age in cases was 36.77 ± 1.26 weeks and in healthy neonates was 36.60 ± 1.75 weeks. Among late preterm newborns, there were 15 septic cases and 16 non-septic cases with a non-significant p-value (0.8). 51% of the sepsis cases were SGA, while the rest 49% were AGA (p value 0.27). No significant association of gender with sepsis (p = 0.8) was observed. Mode of delivery had no significant correlation with neonatal sepsis, as evident by a p value of 0.3. A statistical significance was observed between the place of delivery and sepsis (p value of less than 0.001). 77%

of the septic babies were outborn, which shows that there is a particular need to have a proper segregation between inborn and outborn babies, and there is a particular need to have a proper screening in place for outborn babies. These findings resemble a study by Coggins et al. (2023) [13].

Table 3. Comparison of septic and non-septic group according to vitamin D level

Characteristics	**VDD**	**Adequacy**	χ^2	**P-value**
Culture positive sepsis	21	1	5.6	0.01
Probable sepsis	5	3		
Clinical sepsis	2	2		
EOS	24	3	5.8	0.01
LOS	4	4		
Neonates with sepsis	28	7	6.34	0.02
Neonates without sepsis	18	17		

Regarding the association of vitamin D and neonatal sepsis (Table 3), in our study, 28 neonates with sepsis (80%) were found to have VDD (<20 ng/ml), and the rest, 7 (20%) neonates with sepsis, were found to have adequate vitamin D. A definite correlation (P = 0.02) was found between neonatal sepsis and VDD. There were 22 cases of culture-positive sepsis, out of which 21 cases showed VDD and 2 cases had adequate levels of vitamin D. Among 8 probable sepsis cases, 5 neonates were found to have vitamin D deficiency, and 3 had adequate vitamin D. There were 4 cases of clinical sepsis, out of which 2 cases showed VDD and 2 neonates had adequate levels of cholecalciferol. Among 27 newborns with EOS, 24 neonates had vitamin D deficiency and 3 had adequate vitamin D, while in LOS equal numbers (4) had VDD and adequacy. Among all the kinds of sepsis, culture-positive sepsis (63%) and early-onset sepsis (80% vs. 20% in LOS) were predominant. We found an association of VDD with EOS, which was in line with a study undertaken by Cizmeci et al. [14], where association of hypovitaminosis D with EOS was evident by significantly lower vitamin D levels (median 12.6 ng/mL (3.1-78.9) in the septic neonates than in their non-septic counterparts (median 21 ng/ml with a p value of 0.038).

A significant correlation was established between EOS and VDD. Our study showed that early-onset sepsis had a significant correlation (p = 0.02) with vitamin D deficiency compared to LOS, which was different from a study by Dhandai et al. that showed the case group had significantly lower mean (SD) vitamin D levels [15.37 ng/ml (10.0)] than the control group [21.37 ng/ml (9.53)] (p = 0.001) [53]. The results are parallel with the studies by Terek et al. [19] and Abdelmaksoud et al. [20].

Table 4. Correlation Between Vitamin D Levels and Hospital Stay

Vitamin D Status at Admission	Hospital Stay (Days)	Correlation Coefficient (r)
Sepsis Cases		
Severe Deficiency (<12 ng/ml)	18 ± 5	-0.60
Insufficiency (12-20 ng/ml)	14 ± 4	-0.45
Adequacy (>20 ng/ml)	10 ± 3	-0.30
Controls		
Severe Deficiency (<12 ng/ml)	5 ± 2	-0.20
Insufficiency (12-20 ng/ml)	3 ± 1	-0.15
Adequacy (>20 ng/ml)	2 ± 1	-0.10

In our study, the relationship between vitamin D levels at admission and the duration of hospital stay for both sepsis cases and controls (Table 4) showed that sepsis cases with severe deficiency (<12 ng/ml) had an average hospital stay of 18 ± 5 days, showing a strong negative correlation coefficient (r = -0.60). Similarly, those with insufficiency (12-20 ng/ml) and adequacy (>20 ng/ml) had shorter stays with increasing Vitamin D levels, with correlation coefficients of -0.45 and -0.30, respectively. In contrast, control subjects exhibited shorter hospital stays overall, with severe deficiency, insufficiency, and adequacy displaying progressively shorter stays (5 ± 2 days, 3 ± 1 days, and 2 ± 1 days, respectively), albeit with weaker negative correlation coefficients (-0.20, -0.15, and -0.10, respectively). These findings suggest a potential association between vitamin D status and duration of hospitalisation in both cases of sepsis and controls, with stronger correlations observed in the sepsis cohort. These findings were similar to a study done by Atif et al. (2020) [14], where a positive relation was obtained between the duration of hospital stay in septic patients and VDD. Studies by Dutta et al. (2021) [15] gave a pattern of VDD and type of sepsis in prolonged use. Similar findings were also observed in a study by Madden et al. [17] examining the admission levels of vitamin D in critically ill children, where they discovered a significant prevalence of VDD (40% children). It showed heightened disease severity in children with VDD upon

admission [18] with a longer duration of hospital stay in the sepsis group.

Our findings on duration of hospital stay and antibiotic treatment duration further underline the health disparities between cases and controls, especially noted in the longer stays and more extended treatment durations among cases and the associated vitamin D deficiencies in sepsis cases when the duration of hospital stay or the duration of antibiotic treatment is longer. This highlights the severity of the conditions impacting cases compared to controls.

Table 5. Logistic Regression Analysis Predicting Sepsis based on Vitamin D Levels and Other Clinical Factors

Variables	**coefficient**	**Odds ratio**	**p-Value**
Vitamin D level (per 10ng/ml increase)	0.25	0.78	0.03
Maternal HTN	0.60	1.82	0.05
Premature Birth	1.25	3.49	**<0.001**
Birth weight	0.90	2.46	**0.01**
Male	0.35	1.42	0.10

Logistic regression analysis (Table 5) predicted the likelihood of sepsis based on initial vitamin D levels and other clinical factors. Higher vitamin D levels, with each 10 ng/mL increase, show a significant negative association ($\beta = -0.25$, odds ratio = 0.78, $p = 0.03$) with the outcome. Maternal hypertension ($\beta = 0.60$, odds ratio = 1.82, $p = 0.05$) and premature birth ($\beta = 1.25$, odds ratio = 3.49, $p < 0.001$) are positively associated, indicating increased odds. Similarly, lower birth weight (<2500g) ($\beta = 0.90$, Odds Ratio = 2.46, $p = 0.01$) and male gender ($\beta = 0.35$, Odds Ratio = 1.42, $p = 0.10$) are associated with higher odds of the outcome, though the gender association is not statistically significant at conventional levels.

Conclusion

The study showed a significant association of neonatal sepsis with vitamin D. The study highlights extended hospital stays and increased mortality among septic neonates with vitamin D deficiency. These findings underscore the potential role of vitamin D in influencing recovery rates, shorter hospital stays, and less mortality. Further large-scale studies are required to determine the direction of this association.

Conflict of interest

The authors declares that they do not have conflict of interest.

Ethical Approval

The study was approved by the institutional ethics committee.

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ORIGINAL ARTICLE

Perceptions of Competency-Based Medical Education (CBME) Curriculum Among Indian Medical Students: A Cross-Sectional Analysis from ANIIMS, Port Blair

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Abstract

Introduction: The Competency-Based Medical Education (CBME) curriculum was introduced by the National Medical Commission (NMC) of India in 2019, aiming to bridge the gap between theoretical knowledge and practical skills among medical graduates. This study explores students' perspectives on the CBME curriculum, with a focus on foundational skills, self-directed learning, integration, ethics, and assessment strategies, as experienced by multiple cohorts at the Andaman and Nicobar Islands Institute of Medical Sciences (ANIIMS), Port Blair. **Materials and Methods:** A cross-sectional survey was conducted from April to May 2023 among MBBS students at ANIIMS, covering the 2019-2022 batches. A structured questionnaire was used to gather students' feedback on various CBME components, including foundational courses, learning strategies, integration, ethics, and assessment methods. Descriptive and inferential statistical analyses were performed, with Chi-square tests and ANOVA to examine the association between student responses and their year of joining. **Results:** Out of 144 participants, a high agreement was observed on the importance of foundational components such as Basic Life Support (100%) and Professionalism and Ethics (99%). CBME learning strategies, including Small Group Teaching and Self-Directed Learning, were positively endorsed, though batch-based variations were noted. Significant differences were found in components like Small Group Teaching ($p = 0.048$) and assessment understanding ($p = 0.015$), with newer cohorts showing higher levels of comprehension and appreciation. Integration and ethics were consistently well-regarded across all batches, while challenges were highlighted in areas such as logbook management. **Conclusion:** The CBME curriculum has been positively received by medical students, with newer cohorts demonstrating a greater appreciation for self-directed and integrated learning approaches. However, logistical and educational barriers remain in areas like logbook management and assessment structure comprehension, indicating a need for continued curriculum refinement. This study provides valuable insights into how CBME is perceived by medical students and highlights areas for further enhancement to ensure competency-based training meets the needs of future healthcare professionals.

Keywords: CBME, medical education, competency-based curriculum, medical students, curriculum perception

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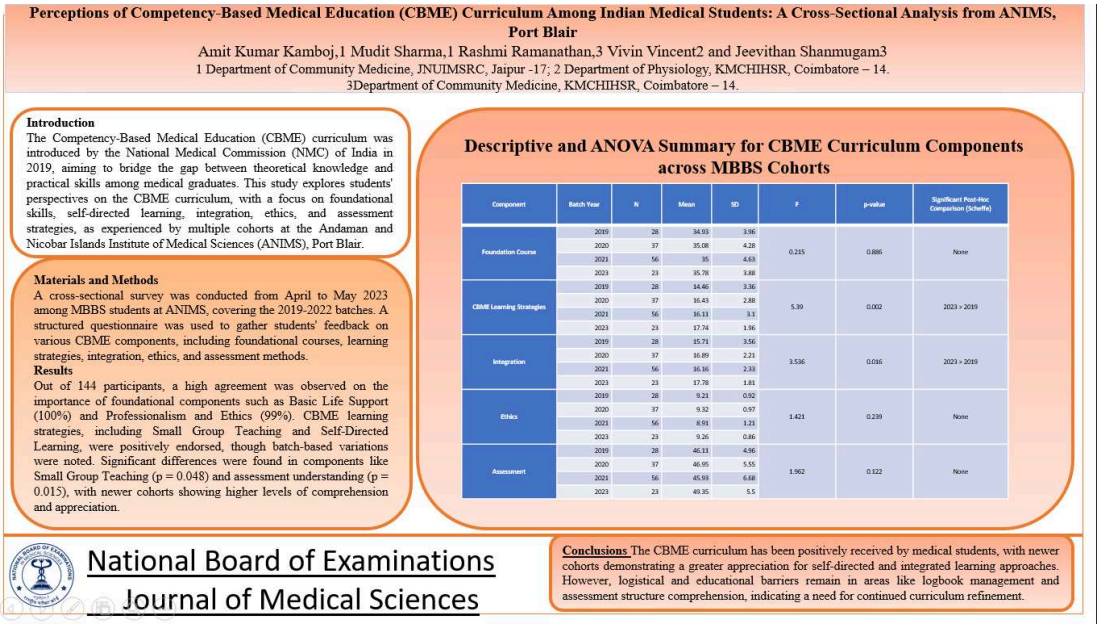
Graphical Abstract



Introduction

The Competency-Based Medical Education (CBME) curriculum, implemented by the National Medical Commission (NMC) in India in 2019, had marked a significant departure from the traditional medical education model. This shift was motivated by the need to produce medical graduates who are not only knowledgeable but also competent in a range of essential skills, including clinical, communication, and ethical decision-making. The traditional curriculum, which focused heavily on theoretical knowledge and standardized testing, often left students with limited practical skills and unprepared for real-world challenges. In contrast, the CBME curriculum emphasizes the development of specific competencies, aiming to bridge the gap between academic training and clinical practice. Recent studies, including our own research, have begun to examine the impact of these changes on students' learning experiences and preparedness for future roles in healthcare [1-5].

The foundation course, integrated teaching, and the use of formative assessments were among the key innovations introduced under CBME, designed to engage students in a more holistic learning process. Early exposure to clinical settings, interdisciplinary teaching, and stress management training, and all hallmarks of the CBME curriculum, were highlighted as beneficial elements by the students. Previous research has shown that such components foster critical thinking, adaptability, and resilience, which are essential traits in the rapidly evolving medical field [1,2,4,5].

One of the key objectives of the CBME curriculum is to produce "globally competent" doctors who can provide high-quality care in diverse healthcare settings. The CBME approach includes structured clinical exposure, early engagement with patients, and emphasis on self-directed learning [1,3]. Students are encouraged to develop reflective practices, which help them evaluate their performance and identify areas for improvement. Formative

assessments, logbooks, and multiple-choice questions are used to monitor students' progress and provide constructive feedback [1-4]. These methods have proven effective in enhancing students' clinical skills and communication abilities, as highlighted in our previous publications [1]. The CBME framework also incorporates a robust ethics and professionalism component, ensuring that students are not only clinically competent but also empathetic and culturally sensitive practitioners [5].

Given these extensive changes, it is essential to gather feedback from students on how the CBME curriculum has impacted their educational journey and professional development. Understanding students' perceptions of the CBME curriculum can offer valuable insights for policymakers, educators, and administrators to further refine and improve the curriculum. Our study, therefore, seeks to add to the growing body of evidence on CBME's effectiveness by capturing student voices from various batches, documenting both the strengths and areas for improvement in the curriculum. By focusing on the experiences and feedback from students, we aim to provide a comprehensive evaluation of how the CBME curriculum aligns with its objectives and how it has been received by those directly involved in the learning process. This feedback is critical to ensure that the curriculum continues to evolve and meet the demands of modern healthcare.

Materials and Methods

This cross-sectional study was conducted over a period of two months, from April to May 2023, among MBBS students at the Andaman and Nicobar Islands Institute of Medical Sciences (ANIIMS), Port Blair. The study aimed to assess the perspectives of medical students on the implementation of the Competency-Based Medical Education (CBME) curriculum introduced by the National Medical Commission (NMC) of India. Ethical approval for the study was obtained from the institutional ethics committee at ANIIMS, ensuring compliance with ethical research standards and safeguarding participant rights.

Students from 2019, 2020, 2021 and 2022 batches were included, and responses were gathered through a structured questionnaire administered during classroom sessions. Students who completed the first MBBS were included in this study. Though the 2023 batch were in the college during the conduct of the study, since they have not completed the first MBBS, they would not be in a position to answer all the components. Hence, they were excluded from the study. The students were explained about the objectives of the study, the need for the study, rights of the students and the other ethical concerns. The Participant information sheet was also given to them. Once they accepted to participate, a written informed consent was obtained, ensuring voluntary participation and confidentiality. The questionnaire addressed various components of the CBME curriculum, focusing on foundational courses, learning strategies, integration, ethics, and assessment methods, capturing the students' views on their benefits and challenges.

The collected data was entered in Microsoft excel and was analysed with SPSS 27 to identify the perceived impact of the CBME curriculum on students' learning and competency development, with a focus on their satisfaction and challenges faced with the curriculum transition. The responses were quantified and analysed to determine the distribution of opinions

across different curriculum components. Basic descriptive data were expressed as frequency/ percentage and Mean ± SD. Chi square test and ANOVA with post hoc scheffe was used to measure the association between various factors and level of agreement.

Results

A total of 144 students participated in the study. The distribution of students by year of joining MBBS reflects a varied representation across four batches: 2019, 2020, 2021, and 2022. The largest group consists of students from the 2021 batch, accounting for 38.9% of the sample, indicating a significant input from this cohort. The 2020 batch follows with 25.7%, while the 2019 and 2022 batches contribute 19.4% and 16.0%, respectively. This distribution demonstrates a steady intake of students over recent years, with a cumulative representation of 84% from the three most recent batches (2019-2021) and a smaller input from the most recent batch of 2022. This balanced representation allows for a comprehensive analysis of student perceptions across different stages of the MBBS curriculum, highlighting any evolving trends or challenges in adapting to the CBME curriculum over these years.

The survey findings indicate a highly positive reception of foundational components and CBME learning strategies among students, with a near-universal endorsement of essential skills and strategies. Specifically, foundational components such as Basic Life Support, Language and Communication Skills, and Professionalism and Ethics garnered agreement rates exceeding 99%, highlighting students' recognition of these elements as essential for their medical education. Components like IT/Computer Skills and Stress Management, while still largely valued, displayed slightly lower agreement levels, particularly IT skills, which had an agreement rate of 91.7%. This variation may reflect differences in individual exposure and the perceived importance of technology in the medical curriculum. Ethics was unanimously recognized as an essential component, with 100% agreement on the necessity of learning ethics, professionalism, and communication in the initial phase of training.

Regarding CBME learning strategies, components such as Early Clinical Exposure and Reflective Learning received strong support, with over 90% agreement. However, Self-Directed Learning showed slightly lower agreement (88.9%), suggesting a possible need for additional guidance or adaptation to this independent learning approach among students. Assessment methods and additional learning supports also received positive feedback. Students acknowledged the role of MCQs, problem-based learning, and elective postings, each receiving over 95% agreement, affirming these as beneficial to their competency development. Notably, the preference for case-based assessments over traditional essay formats suggests a shift toward practical, scenario-based learning. However, only 68.1% agreed on the feasibility of maintaining separate logbooks for each department, indicating logistical challenges or concerns with this approach. Overall, these insights underscore the value students place on foundational skills, interactive learning methods, and scenario-based assessments, with minor areas noted for further enhancement or support. (Table 1)

Table 1. Perception of Students about CBME curriculum

S.No	Parameter	Agree		Disagree	
		F	%	F	%
Useful Components of Foundation Course					
1	Basic Life Support	143	99.3	1	0.7
2	Field / Health Centre Visits	142	98.6	2	1.4
3	Time Management	142	98.6	2	1.4
4	Stress Management	141	97.9	3	2.1
5	Language & Communication Skills	143	99.3	1	0.7
6	Professionalism and Ethics	143	99.3	1	0.7
7	Biomedical Waste Management	142	98.6	2	1.4
8	IT/Computer Skills	132	91.7	12	8.3
CBME Learning Strategies					
9	Self-Directed Learning	128	88.9	16	11.1
10	Early Clinical Exposure	141	97.9	3	2.1
11	Reflective Learning	135	93.8	9	6.3
12	Small Group Teaching / Learning	133	92.4	11	7.6
Assessment and Integration					
13	Multiple Choice Questions have their own role in assessment	137	95.1	7	4.9
14	Assessment using Problem-Based Learning and Case Scenarios improves competency	142	98.6	2	1.4
15	Elective posting is needed after Phase III	137	95.1	7	4.9
16	It is possible to maintain separate log books for each department	98	68.1	46	31.9
17	Phase I in medical college is academically very stressful	141	97.9	3	2.1
18	There should be some time for sports activities during weekdays	142	98.6	2	1.4
19	After three years of CBME implementation, I am well-versed in all its components	122	84.7	22	15.3

20	Assessment in the form of case scenarios instead of essays and short essays is preferable	137	95.1	7	4.9

Chi-square test was done to provide insights into MBBS students' perspectives on the foundation course and CBME curriculum components across various batches. The cross-tabulated analysis of various foundational components and learning strategies, categorized by MBBS batch years, reveals high consistency in positive responses across all batches regarding the perceived benefits of foundational course elements. Notably, 100% of students across batches agreed on the necessity of Basic Life Support training, with slight variations observed in components such as Field/Health Centre visits and Time Management. A small percentage of students from the 2019 and 2021 batches (3.6% and 1.8%, respectively) disagreed with the utility of Field/Health Centre visits. However, overall, above 98% across batches positively endorsed these components. Similarly, IT/Computer Skills saw a broader range in agreement, with the 2019 batch showing a slightly lower endorsement (85.7%) compared to other batches.

In CBME learning strategies, batch-based differences were observed in the endorsement of Self-Directed Learning, with the 2019 batch showing a lower agreement rate (78.6%) compared to the 2021 batch (91.1%) and the 2023 batch (100%). A chi-square test revealed significant batch-based differences for some strategies, such as Small Group Teaching/Learning, where the 2019 batch had a lower agreement rate (82.1%) compared to others ($p = 0.048$). Additionally, significant batch differences were observed in understanding of assessment systems ($p = 0.015$), with earlier batches (notably the 2019 cohort) reporting lower levels of comprehension in comparison to more recent cohorts, potentially reflecting challenges in initial curriculum adaptation. Integration elements, including horizontal and vertical integration, were generally well-received across batches, with over 98% agreement, indicating a shared positive perception of integrated learning across subjects among students from all cohorts. These findings highlight that while positive reception to CBME components and strategies is strong across batches, minor batch-specific preferences and challenges exist, potentially linked to varying levels of curriculum adaptation over time. (Table 2)

Table 2. Perception of Medical Students on the Importance of CBME Components Across Batches

S.No	Parameter	2019		2020		2021		2022		p-value
		N	%	N	%	N	%	N	%	
		Frequency and Percentage of those who agree the importance								
1	Basic Life Support	28	100	37	100	56	100	23	100	0.663
2	Field / Health Centre Visits	27	96.4	37	100	55	98.2	0	0	0.597
3	Time Management	28	100	36	97.3	55	98.2	0	0	0.741
4	Stress Management	26	92.9	36	97.3	56	100	0	0	0.153
5	Language & Communication Skills	28	100	36	97.3	56	100	0	0	0.405
6	Professionalism and Ethics	28	100	37	100	55	98.2	0	0	0.663
7	Biomedical Waste Management	26	92.9	37	100	56	100	0	0	0.038
8	IT/Computer Skills	24	85.7	35	94.6	52	92.9	2	8.7	0.61
9	Self-Directed Learning	22	78.6	32	86.5	51	91.1	23	100	0.095
10	Early Clinical Exposure	27	96.4	37	100	54	96.4	23	100	0.534
11	Reflective Learning	25	89.3	34	91.9	53	94.6	23	100	0.427
12	Small Group Teaching / Learning	23	82.1	33	89.2	54	96.4	23	100	0.048
13	Multiple Choice Questions have their own role in assessment	25	89.3	35	94.6	54	96.4	23	100	0.324
14	Assessment using Problem-Based Learning and Case	28	100	36	97.3	55	98.2	23	100	0.741

	Scenarios improves competency									
15	Elective posting is needed after Phase III	27	96.4	35	94.6	55	98.2	20	87	0.204
16	It is possible to maintain separate log books for each department	17	60.7	24	64.9	38	67.9	19	82.6	0.375
17	Phase I in medical college is academically very stressful	28	100	37	100	53	94.6	23	100	0.186
18	There should be some time for sports activities during weekdays	28	100	37	100	54	96.4	23	100	0.364
19	After three years of CBME implementation, I am well-versed in all its components	22	78.6	29	78.4	50	89.3	21	91.3	0.303
20	Assessment in the form of case scenarios instead of essays and short essays is preferable	26	92.9	36	97.3	53	94.6	22	95.7	0.866

The responses were converted into scores and the mean score between the groups were analysed to find out the association if any, the analysis of different MBBS cohorts reveal consistent and insightful patterns regarding perceptions of the CBME curriculum components. Across all batches, the foundation course received similar mean scores with no significant differences, indicating a consensus among students on the foundational aspects of CBME, valued consistently across years of joining. This uniformity points to a shared positive perception of the course's essential elements among students, regardless of batch differences.

However, some variations emerged in other areas. For instance, CBME learning strategies were viewed significantly more favourably by the 2023 batch compared to earlier cohorts, particularly the 2019 batch. This could signal a growing appreciation of self-directed and interactive learning approaches, possibly as students become more accustomed to CBME over time. Similarly, integration components such as

horizontal and vertical integration showed higher endorsement in the newer 2023 batch compared to earlier ones, with the 2023 batch reporting the highest mean score (17.78) and the 2019 batch the lowest (15.71). This trend suggests an evolving perspective in favor of integrated learning as curriculum adjustments enhance its effectiveness.

In other curriculum areas, such as ethics, no significant differences were observed across batches, which suggests stable attitudes toward ethical training as a core component of early medical education. Although not statistically significant, assessment mean scores have shown a slight upward trend, with the 2023 cohort rating this component higher, possibly reflecting increased familiarity with the CBME assessment structure. (Table 3)

Table 3. Descriptive and ANOVA Summary for CBME Curriculum Components across MBBS Cohorts

Component	Batch Year	N	Mean	SD	F	p-value	Significant Post-Hoc Comparison (Scheffe)
Foundation Course	2019	28	34.93	3.96	0.215	0.886	None
	2020	37	35.08	4.28			
	2021	56	35	4.63			
	2023	23	35.78	3.88			
CBME Learning Strategies	2019	28	14.46	3.36	5.39	0.002	2023 > 2019
	2020	37	16.43	2.88			
	2021	56	16.11	3.1			
	2023	23	17.74	1.96			
Integration	2019	28	15.71	3.56	3.536	0.016	2023 > 2019
	2020	37	16.89	2.21			
	2021	56	16.16	2.33			
	2023	23	17.78	1.81			
Ethics	2019	28	9.21	0.92	1.421	0.239	None
	2020	37	9.32	0.97			
	2021	56	8.91	1.21			
	2023	23	9.26	0.86			
Assessment	2019	28	46.11	4.96	1.962	0.122	None
	2020	37	46.95	5.55			
	2021	56	45.93	6.68			
	2023	23	49.35	5.5			

Discussion

The implementation of Competency-Based Medical Education (CBME) by the National Medical Commission (NMC) in India marks a transformative shift from traditional time-based training to an outcome-based framework that focuses on equipping medical graduates with essential competencies required for effective medical practice [1-4]. This shift resonates with global trends in medical education, where the emphasis on competency and practical skill integration has demonstrated benefits in improving medical outcomes [6-10]. However, the integration and acceptance of CBME have varied, as observed in this study's cohort-based analysis of students' perspectives on foundational, integrative, and evaluative components of the CBME curriculum [11].

Students across batches showed strong endorsement for foundational skills, especially in areas such as Basic Life Support (BLS) and Professionalism, which aligns with previous findings that stress the need for medical graduates to be well-versed in essential clinical skills early in their training [12]. This result echoes the findings of Epstein and Hundert, who emphasized the importance of competence in communication, ethics, and patient care as fundamental to medical education [13]. The consistently high agreement rates on foundational skills highlight the effectiveness of CBME's initial phases, which prioritize these critical competencies [14].

Despite high acceptance of foundational components, disparities emerged in students' reception of CBME's learning strategies, particularly Self-Directed Learning (SDL) and Small Group Learning. Earlier cohorts, like the 2019 batch, expressed lower favorability towards SDL, which may indicate challenges in adapting to a more autonomous learning model [15]. This outcome is supported by previous research, where transition to self-directed formats has been shown to necessitate additional guidance and support structures, especially for students accustomed to structured learning environments [16]. Small Group Teaching, while highly valued, also revealed cohort differences, with lower endorsements from the earlier 2019 cohort, suggesting an initial adaptation phase that could benefit from better preparatory or support systems [1].

The need for integration in CBME, covering both horizontal and vertical integration across subjects, was recognized positively across cohorts, though more recent batches (2022 and 2023) rated this aspect higher. Harden et al. suggested that integrating topics across disciplines facilitates holistic learning, which helps students contextualize knowledge [17]. These findings align with the research by ten Cate, which showed that integration enhances knowledge retention and applicability in clinical settings [18]. However, student feedback on the time-consuming nature of integration sessions indicates that careful attention is needed to balance depth with manageability in the curriculum [19].

In terms of assessments, while traditional assessments received positive feedback, there was strong student preference for problem-based and case-based assessment formats over essays. The literature supports this shift, as case-based assessments promote critical thinking and are aligned with CBME's goals of producing competent, practice-ready graduates [20-21]. The observed challenges with maintaining separate logbooks across

departments reflect logistical issues and suggest a need for more streamlined documentation processes to ensure these tools enhance rather than hinder the learning experience.

Conclusion

The CBME curriculum, as perceived by medical students across multiple cohorts, reflects a positive response towards foundational skills, interactive learning strategies, and integrated assessment methods. The study highlights that newer cohorts have a greater appreciation for self-directed and integrated learning approaches, suggesting that curriculum adaptations over time have made these methods more effective and accessible. However, challenges remain in areas such as logbook management and comprehension of assessment structures, emphasizing the need for continuous curriculum refinement to address logistical and educational barriers. This research contributes to the understanding how CBME is perceived and utilized in Indian medical education and suggests that further refinement of student-centered strategies may enhance the effectiveness of competency-based training.

Statements and Declarations

Ethical Approval

Ethical approval for the study was obtained from the institutional ethics committee at ANIIMS, ensuring compliance with ethical research standards and safeguarding participant rights.

Conflicts of interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

Evaluation of the Structural and Functional Dynamics of Extracellular Matrix of the Skin and Histochemical Characterization of the Dermal Interstitium

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Abstract

Introduction: Skin is the largest organ in the body consists of three layers, epidermis, dermis and hypodermis. Skin along with its accessories like nails, hair follicles, sweat glands and sebaceous glands forms the integumentary system. Skin acts as a barrier between the external factors and internal environment and gives protection to deeper tissues in the body. Skin cancer is the fifth most common type of cancer. **Materials and Methods:** Samples for this study were taken from human cadavers. Histochemical study was done with Van Gieson's method for collagen fibers, Weigert's resorcin fuchsin for elastic fibers and Mallory's trichrome stain for connective tissue were used to study the connective tissue. Collagen, elastic fibers and cells in the interstitium of skin were analyzed. **Results:** Thick and thin collagen fibers were found to be arranged in vertical and horizontal direction in the dermis. Mast cells and macrophages were more in number in the interstitium near the vessels. Fibers surrounding the vessels transfer the mechanical pressure to the lymphatic vessels. Initial and collecting lymphatic vessels were identified. **Conclusion:** The arrangement of fibers and distribution of cells in the skin helps in understanding fields like regenerative medicine and tissue engineering.

Keywords: Skin, Interstitium, histochemistry, lymphatics, interstitial space

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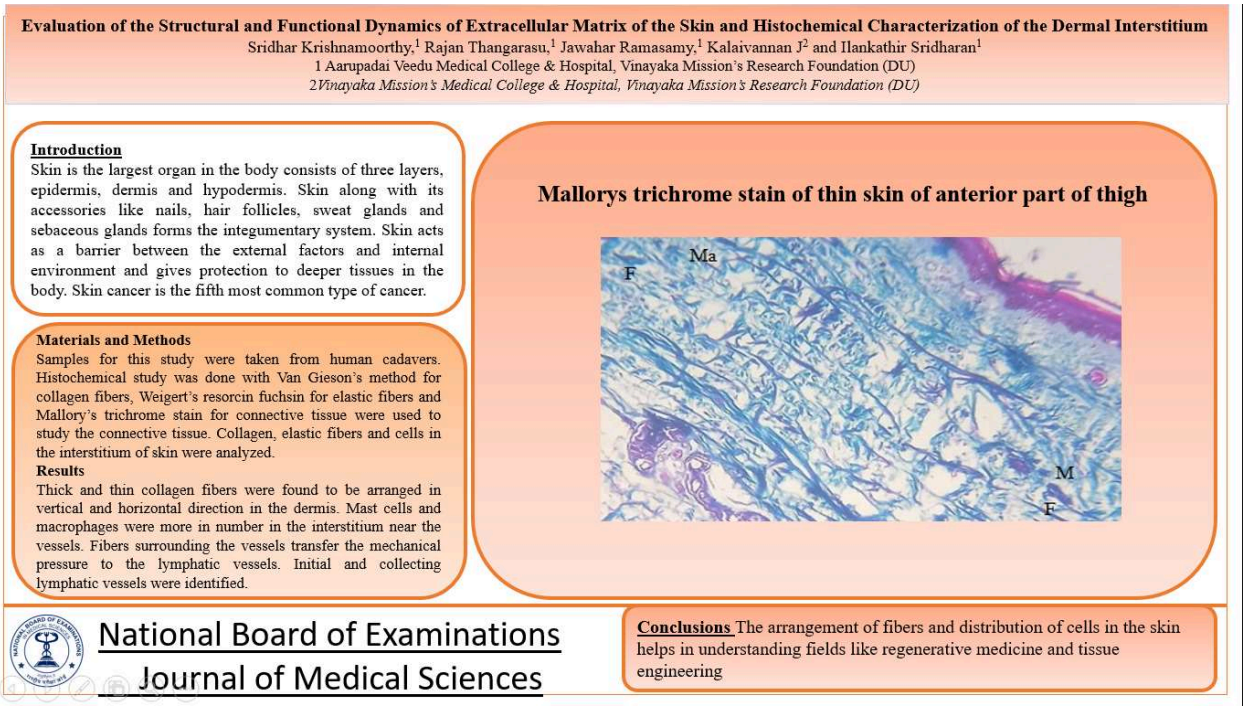
Graphical Abstract



Introduction

Human skin is the largest organ, made up of three layers, epidermis, dermis and hypodermis. There are two types of skin, thin skin and thick skin. Outermost layer is epidermis, formed by stratified squamous non keratinized epithelium and is avascular in nature. Developmentally ectoderm layer gives rise to epidermis. Dense irregular connective tissue forms the dermis and is richly supplied with blood vessels and nerves. The connective tissue of both thin skin and thick skin consists of interstitial space in the interstitium. The structure and function of the skin is maintained by the extracellular matrix (ECM), cells and fibers. The ECM is a compound arrangement of macromolecules such as proteins, polysaccharides and adhesion molecules, which provides mechanical support and allows the passage for biochemical signals to the surrounding cells [1]. Fibroblast, Adipocytes (fat cells), mast cells and macrophages are the cells present in the connective tissue matrix. Along with these cells undifferentiated multipotent mesenchymal cells are present. Fibroblasts are the primary cells responsible for the production of ECM and the structural proteins are collagen, elastic and reticular fibers. Collagen provides firmness and tensile strength and elastic fibers allows the skin to widen and recoil by its elastic property. The gel like ECM is due to the hydration of hyaluronic acid present in proteoglycans and glycosaminoglycans [2]. Mast cells and macrophages are the immune cells respond directly to any infections, injuries or irritation of skin and both cells remove the pathogens, dead cells and regulate the tissue repair. Reticular fibers

forms mesh work like structure and support the surrounding cells and tissue.

Superficial part of the dermis is papillary layer made up of loose areolar tissue and it produces finger like projection into the epidermis called papillae [3]. Deeper layer of the dermis is called reticular layer formed by dense irregular connective tissue. The collagen fibers extend into the hypodermis for anchoring. Hypodermis is a loose areolar tissue consists of more adipose cells and also called as superficial fascia. Adipose cells store fat and provide insulation and cushioning effect for the skin. The space between the cells and fibers in the connective tissue is called as interstitial space. Fluid present in this space is called as interstitial fluid. The interstitial fluid provides a medium for the exchange of nutrients and waste materials between the blood vessels and cells.

Skin along with its accessories like nails, hair follicles, sweat glands and sebaceous glands forms the integumentary system. Skin plays a vital role and gives protection to deeper tissues in the body. Continuous exposure to ultra violet radiation causes melanoma and non melanoma skin cancer. Skin cancer is the fifth most common type of cancer worldwide with increasing incidence [4]. Skin produces vitamin D3, cholecalciferol from 7-dehyrocholesterol on exposure to ultra violet radiation [5]. Skin may be affected by melanomas, cancer and some genetic diseases like albinism and vitiligo. The fluid and structural atmosphere around cells is provided by the interstitial space that exists between blood arteries and cells. The fluid from the circulatory area continuously filters by means of microvessels through the interstitial space in most tissues under normal circumstances, without being reabsorbed [6]. Clinically some drugs are given through skin in topical routes [7]. Interstitium apart from providing a structural support, it also acts as a medium for transport of fluid and immune cells.

The purpose of this study is to identify the interstitium as dynamic structure, the extra cellular matrix and its significant role in fluid transport and immune cell trafficking. Understanding the function of the interstitium may help in identifying the process behind frequent skin disorders like inflammation, fibrosis and edema. The interstitium located beneath the skin is continuously exposed to infections and environmental assaults. Moreover, since the interstitium has a direct connection to the lymphatic system, studying its function may reveal the connections between the disorders such as cancer metastasis, autoimmune disorders and the interstitial space of the skin.

In the present study, we have studied the fibers and cells in the interstitium of skin involved in immune surveillance. Knowledge of interstitium helps in disease pathology, immune response, wound healing process, tissue regeneration and possible clinical applications in the management and prevention of skin associated disease conditions.

Materials and Methods

Histochemical study was conducted on the human cadaver skin. Skin samples were collected from both male and female. Samples were obtained from scalp, arm,

front of thigh, pectoral region and anterior abdominal wall. Study design was experimental study, conducted in department of Anatomy, Aarupadai Veedu Medical College & Hospital, Pondicherry, India. Ethical clearance was obtained from the Institution ethical committee (AV/IEC/2022/023).

Tissue Processing

Human skin tissues were obtained from both male and female cadavers. The tissues were processed for light microscopy. To prevent putrefaction and autolysis the collected tissues were fixed in formal saline at room temperature. Formal saline contains 50ml of formalin, 450ml of water and 1.8g of sodium chloride. After primary fixation, tissues were washed under running tap water overnight. Dehydration was done by passing the tissues from ascending grade of 50% to absolute isopropyl alcohol. Clearing was done with two changes in xylene. Infiltration was done with paraffin wax at 60^0C in wax bath. Each tissue was embedded in separate paraffin block. The sections were taken in rotary microtome of 5µm thickness. The sections were taken in clean glass slide.

Histochemical staining

Van Gieson's method for collagen fibers

Van Gieson Solution was prepared by mixing 100ml of saturated aqueous picric acid solution with 10ml of 1% aqueous acid fuchsin solution. To this 100ml of distilled water was added. Procedure: The sections were deparaffinized in xylene for 5 minutes with two changes. The slides were dipped in descending grades of alcohol and washed in water. Nuclei were stained by the Celestine blue-hematoxylin sequence. Differentiated with 1% acid alcohol and washed in tap water. Counterstained in Van Gieson solution for 3 minutes and dehydrated through ascending grades of alcohol. Cleared in xylene and mounted with DPX [8].

Weigert's resorcin fuchsin for elastic fibers:

Preparation of reagents: 1 g of basic fuchsin and 2 g of resorcin was added to 100 ml of distilled water. Boiled and 12.5 ml of freshly prepared 30 % ferric chloride solution was added. Boiling continued for 5 minutes. Cooled and filtered, and the filtrate was discarded. The whole precipitate was dissolved in 100 ml of 95% ethanol using water bath and 2 ml of concentrated hydrochloric acid was added. The precipitate in a solvent prepared by mixing 50ml of 2-methoxyethanol with 50ml of distilled water. To this 2ml of concentrated hydrochloric acid was added. Procedure: Sections were deparaffinized and taken to alcohol. Slides were placed in resorcin fuchsin solution for 3 hours at room temperature and rinsed in tap water. Background staining was removed by treating with 1% acid alcohol. Rinsed in tap water. Counterstained with Van Gieson solution and dehydrated through ascending grades of alcohol. Cleared in xylene and mounted [8].

Mallory's trichrome stain for connective tissue

Reagents prepared were Acid fuchsin: 1g of acid fuchsin and 0.9g of Biebrich scarlet was added with 100ml of

distilled water. Phosphomolybdic acid: 1g of phosphomolybdic acid was mixed with 100ml of distilled water. Orange G: Orange G 2g, Oxalic acid 2g and Aniline blue 0.5g was added to 100ml of distilled water. Procedure: The slides were deparaffinized with Xylene and the sections brought to water. Slides were kept in acid fuchsin solution for 2 minutes and rinsed with the distilled water. Again the slides were dipped in phosphomolybdic acid for 2minutes and washed in distilled water. Sections were kept in orange G solution for 15 minutes. Slides were washed in running tap water and dehydrated with ethanol. Cleared with xylene and mounted [8].

Results

Histochemical analysis of skin samples were analyzed for the pattern of arrangement of fibers and formation of interstitial space and its importance. In the reticular part of dermis, thick collagen fibers are found to be horizontally arranged and between the horizontal fibers thin collagen fibers are arranged vertically. Interstitial spaces are found between the collagen fibers. Fibroblasts (F) were found nearer to the mast cells (M) and macrophages (Ma). Arterioles and venules are more in number in the papillary part of dermis (Figure 1).

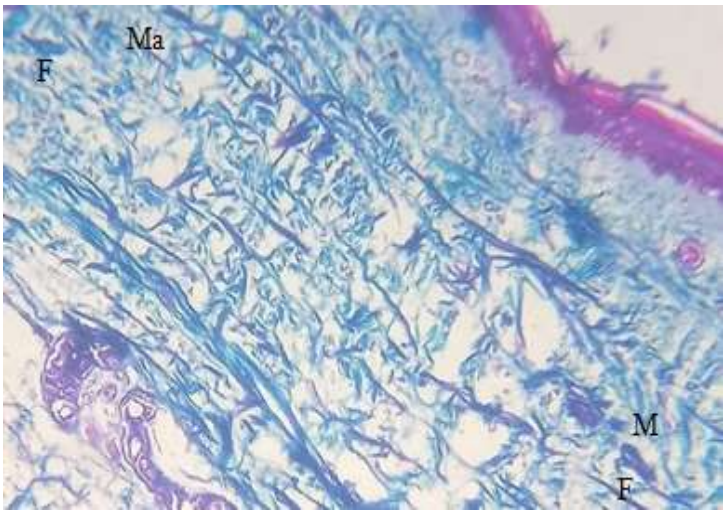


Figure 1. Mallorys trichrome stain of thin skin of anterior part of thigh.

Below the dermis, lymph collecting space (Ls) was present. From this space the lymphatic collecting channel (Lc) was draining the fluid in oblique direction between the adipose cells of hypodermis. It drains into another area present in the lymphatic space above deep fascia (Df). Between the adipose tissue mast cells (M) and macrophages (Ma) were present nearer to each other (Figure 2).

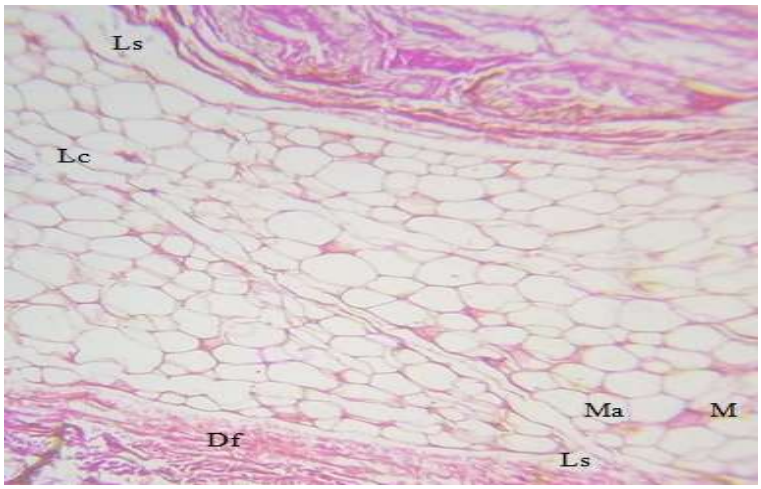


Figure 2. Thin skin of pectoral region stained with resorcin.

Hypodermis consisting of polyhedral adipose cells Lymphatic collecting vessels (Lc) was observed in the hypodermis. They are found to be formed by endothelium. Under the dermis lymphatic space (Ls) were observed which collects fluid from the interstitial space in the dermis. Macrophage (Ma) and fibroblast (F) was found in the dermis and hypodermis. Dendritic cell (D) also found in the dermis (Figure 3).

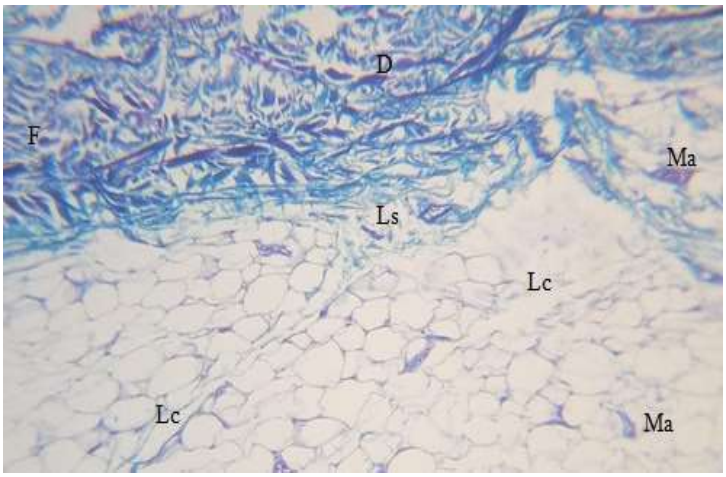


Figure 3. Mallorys trichrome staining of skin of pectoral region.

In hypodermis (Figure 4) the adipose tissue was surrounded by lymphatic space (Ls) formed by collagen fibers. Around the artery, thin collagen fibers (Cf) are arranged in a circular manner forming the interstitial space. Near the artery (A) smaller lymph vessels (Lv) are found. In the dermis the thick collagen fibers are arranged both vertically and horizontally forming the interstitial space. Dendritic cell (Dc) was found near the mast cell. Fibroblast (F) was observed in the interstitial space.

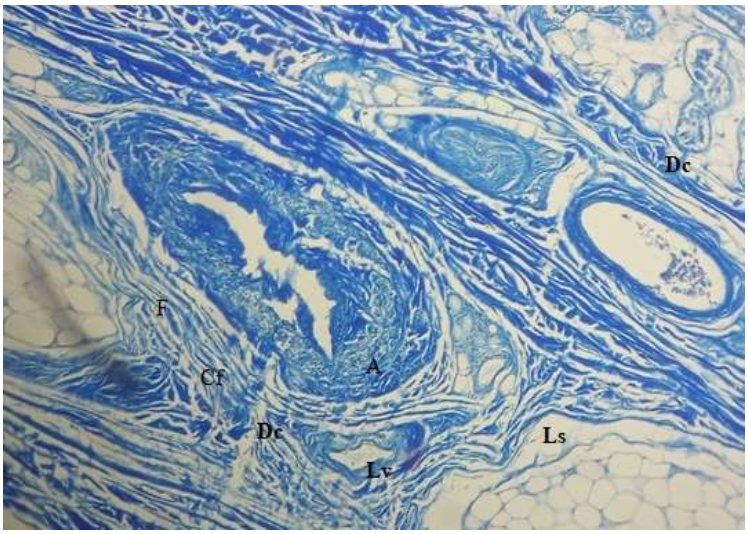


Figure 4. Mallory trichrome stain of abdomen skin.

Van Gieson stain of scalp shows thick collagen fibers arranged horizontally below the epidermis (Ep). Papillary layer (Pl) was not prominently projecting into the under surface of epidermis. More number of fibroblast (F) was present in the papillary layer. We observed a small space below the epidermis and found to be interstitial space. Hair follicle was present in the dermis. Macrophage (Ma) was present near the hair follicle. The collagen fibers are vertically arranged throughout the entire dermis. Few elastic fibers are present in horizontal direction. Between the fibers, wide spread interstitial space was present. A long lymphatic vessel (Ll) with endothelium was observed passing through the entire layer of dermis which is draining into another large vessel (Figure 5).

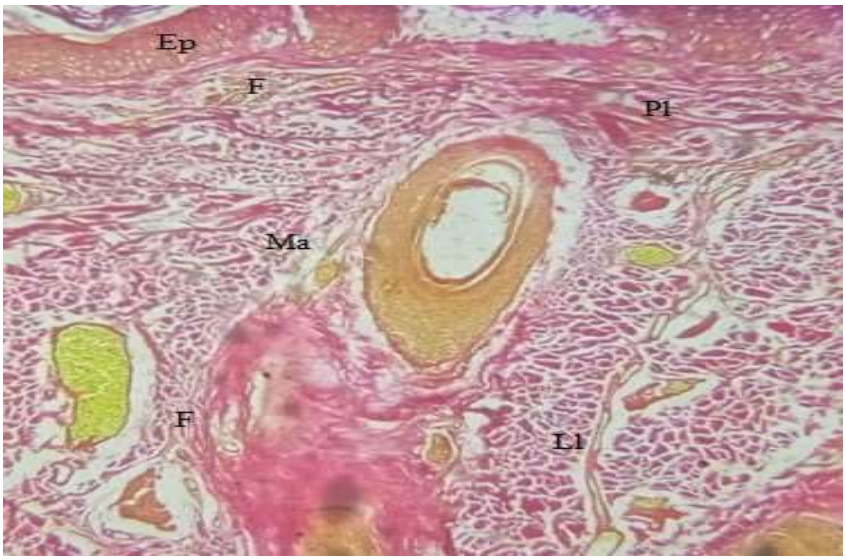


Figure 5. Scalp stained with Van Gieson stain

Collagen fibers were arranged in both horizontal and vertical direction. Sweat glands (Sg) were also surrounded by interstitial space. Macrophages (Ma) were found near the sweat glands. Surrounding the veins (V) and arteries (A) interstitial space was present. In the interstitial space smaller arterioles, venules and lymphatic vessels were found. Fibroblast and mast cells were present in the interstitial space. Interstitial space in the dermis was directly connected to the interstitial space around the vessels. Larger lymphatic space (Ls) was found which drains into lymphatic vessels (Lv) (Figure 6).

Figure 6. Mallorys trichrome staining of thin skin of shoulder.

The sebaceous gland (Se) was surrounded by thick collagen fibers arranged as bundles with thin interstitial space. Sebaceous duct (Sd) was observed near the gland. Arrector pili muscle (Ap) was present nearer to the sebaceous gland. Arrector pili muscle compresses the gland to release the sebum from the gland. In between the collagen fibers numerous smaller arterioles and venules are more in number. Mast cells (M) and macrophages (Ma) were more in number around the sebaceous gland confirms the existence of interstitial space around the gland. Our observation suggests the collagen fibers surrounding the sebaceous gland may compress the gland to release the secretion. Collagen fibers are arranged irregularly and connected by thin elastic fibers in the dermis (Figure 7).

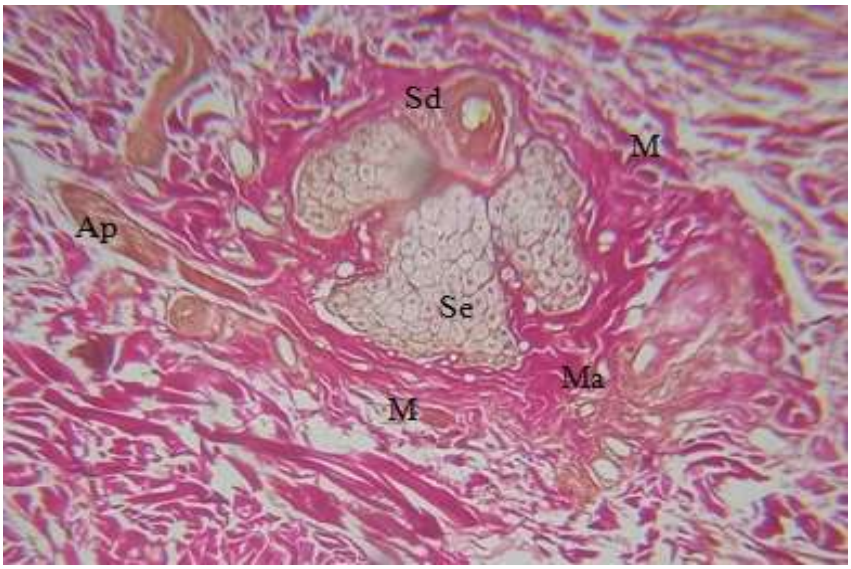


Figure 7. Skin of arm stained by Van Gieson.

Discussion

Rudolf Virchow in 1858 identified that fibroblast was present in the connective tissues [9]. Fibroblast is a spindle shaped cell present in the interstitial space of dermis part of the skin. Fibroblast has abundant rough endoplasmic reticulum by which it actively secretes extracellular matrix and proteins [10]. We observed more number of fibroblast in thick skin and less number of fibroblast in thin skin. In a study conducted on keratinocyte proliferation the researchers identified that fibroblast secretes keratinocyte growth factor and granulocyte macrophage colony stimulating factor and acts as paracrine regulator [11]. Fibroblast also directly communicates with the immune cells in the interstitium. The extracellular matrix (ECM), is the collective term for the structural components of the interstitial space, mostly composed of glycosaminoglycans, elastic fibers, collagen fibers, and microfibrils [12]. ECM withstands mechanical pressure and protects from minor trauma. Elastic and collagen fibers in dermis are produced by fibroblast. Another study suggests that Smooth muscles, endothelial and adventitial cells found in the vessel wall also produce collagen [13]. The elastic and collagen fibers by mechanical contraction exert pressure to the smaller arterioles and venules to manage the interstitial fluid pressure and interstitial fluid volume. This may be due to the basket weave like network of collagen fibers. Depending on the elastin quantity there are three types of elastic fibers in skin namely, elaunin oxytalan and mature elastic fibers. Oxytalan fibers are present near the dermoepidermal junction, elaunin fibers are found in the papillary layer and mature elastic fibers are present in the reticular layer [14]. Presence of elastic fibers in the reticular layer makes the skin to maintain its elasticity and recoil to its original position [15]. There are two types of elastic fibers, vertical elastic fibers reaches upto the basement membrane of epidermis and horizontal fibers are present in the reticular layer of the dermis [16]. Elastic fibers are in

close contact with the interstitial cells and involved in cell proliferation, migration and differentiation. Further elastic fibers are also involved in regulation of cellular phenotypes, production of matrix and cytokines [17].

The collagen fiber being thick in nature has the capacity to pass on the energy during mechanical stress and provides resistance. We found thin collagen fibers at the junction of epidermis and papillary layer and thick collagen fibers are predominantly present in the deeper layers of dermis which is similar to another study [18]. We have also observed thick collagen fibers are horizontally present in the thigh region whereas in the shoulder area the collagen fibers are in vertical direction. Collagen fibers help in migration of cells, morphogenesis of the tissue, involves in tissue repair and regulates the function of inflammatory and resident cells [19]. Collagen and elastic fibers are densely packed in thick skin to withstand mechanical stress whereas in thin skin collagen and elastic fibers are loosely arranged to permit broad range of motion.

The interstitial fluid formed in the interstitial space is removed by the lymphatic vessels and returned to the venous blood. Lymphatic vessels play major role in the interstitium in maintaining the fluid transport, proteins and immune cells. The lymphatic vessels are anchored to the extracellular matrix. The interstitial fluid formed also referred as lymph, is collected by initial lymphatics which starts as a blind end formed by endothelial cells and without basement membrane. We have observed the lymphatic vessels in hypodermis were passing in oblique direction. The muscle contraction and external force on the skin may cause pressure on the oblique lymphatics to drain the interstitial fluid towards the lymph node. The fluid then transferred to collecting lymphatic vessel and drained into lymph trunk. Another study on adaptive immunity suggests that the endothelium of lymphatic vessels control its own flow and communicates with the immune cells [20]. The interstitial space allows the exchange of gas, nutrients and waste products for maintaining the homeostasis.

Macrophages are the first line of defense mechanism. During any type of tissue injury or inflammation it migrates to that particular area and involve in phagocytosis [21]. Paul Ehrlich first coined the term mast cells in 1878 [22]. Mast cells are present mostly in the connective tissue closer to the blood vessels. Heparin and histamine are the secretory granules present in the mast cells [23]. Histamine is formed after the removal of the carboxyl group from the amino acid histidine by the enzyme histidine decarboxylase. Histamine H_1 receptors act on the skin to produce allergic reactions. H_1 receptor is present in chromosome 3 at 3p25 location [24]. Histamine acts on the endothelial lining of the blood vessels causing weakness in between the endothelial cells. Due to this action, cells and proteins leak into the surrounding connective tissues.

Steinman and Cohn in 1973 discovered the dendritic cells from the mouse spleen [25]. Dendritic cells are produced in bone marrow and have the capacity to migrate to other parts of the

body. It has multiple cytoplasmic processes. Dendritic Cells are heterogeneous groups of leukocytes. Dendritic cell identifies the pathogens and are called as antigen presenting cells. The lymphatic vessels transfer the dendritic cells to the circulation through lymph node. Capturing, analyzing, and distributing antigens to stimulate T-cell activation and differentiation, dendritic cells constitute a diverse group of cells that mediate the relationship between the innate immune response and the adaptive response [26]. The macrophages and lymphocytes escape from the capillaries and circulate in the interstitial space. During any inflammation these cells move towards the epidermis for immunological action and in normal stage the cells will move towards lymphatic channels then to regional lymph nodes. Along with the immune cells extracellular sodium ions are stored in the interstitium for the regulation of blood pressure [27].

Conclusion

The interstitium of the skin plays an important role in the protection and maintain equilibrium of the body by regulating the volume and composition of the interstitial space. During inflammation the interstitium gives free space to circulate large proteins and immune cells. Collagen and elastic fibers involves in proliferation of cells, angiogenesis and wound healing. Further the pattern of arrangement of fibers, distribution of cells and lymphatic vessels helps in understanding fields like regenerative medicine, tissue engineering and suggest that the interstitium may function as organ.

Ethical Approval

Ethical clearance was obtained from the Institution ethical committee (AV/IEC/2022/023).

Funding

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Conflicts of interest

The authors declare that they do not have conflict of interest.

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ORIGINAL ARTICLE

Physical Activity Levels and Exercise Perceptions in Overweight and Obese Women

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Abstract

Objectives: Physical activity (PA) is a crucial component of a healthy lifestyle, with numerous benefits for overall well-being and the prevention of non-communicable diseases (NCDs). Physical activity by its ability to boost our immune system can also reduce the burden of communicable disease. Although there is considerable knowledge and research about barriers to activity, the level of physical inactivity and obesity is on a steep rise. Indicating that the interventions in place do not effectively target the barriers and a failing exists to recognize other factors influencing inactivity. The objective of this study is to investigate the levels of physical activity and the perceived benefits and barriers to exercise among overweight and obese women. **Methods:** This descriptive observational cross-sectional study involved 96 women aged 18-64 years. They underwent clinical examinations, BMI and body fat parameters were assessed. Global Physical Activity Questionnaire (GPAQ) and Exercise Benefits and Barrier scale were administered. GPAQ evaluates physical activity across various domains, while EBBS gauges individuals' perceptions of exercise benefits and barriers. **Results:** We found that 34.3% of the participants were physically inactive, 27.08% were moderately active, and 38.5% were highly active based on their MET scoring on the GPAQ questionnaire. Time spent on household chores and workplace attributed to most of the physical activity performed. The subjects were aware of the benefits of exercise. Time restraint, and viewing exercise as tiresome or hard work rather than a form of entertainment were some of the barriers. **Conclusion:** The physical inactivity among overweight and obese women was found to be 34.3%. Lack of time and personal fatigue was cited as being one of the major limiting factors to performing exercise. Interventions targeting these barriers as well as strategies that target the way exercise is perceived by the population, need to be initiated to enhance the levels of physical activity.

Keywords: Physical activity, Overweight women, Obese women, Global Physical Activity Questionnaire (GPAQ), Exercise Benefits and Barriers Scale (EBBS)

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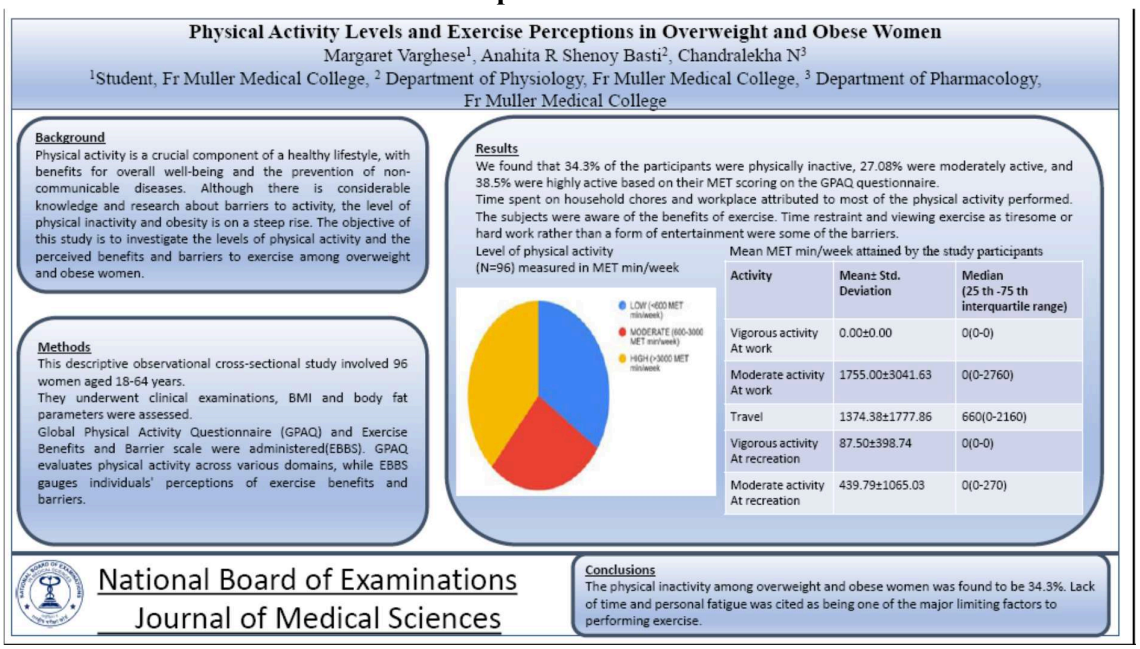
Graphical Abstract



Introduction

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that require energy expenditure, which includes exercises and activities undertaken while working, playing, and carrying out household work [1]. Regular physical activity has been shown to enhance quality of life, while insufficient physical activity is recognized as a major risk factor for mortality and morbidity worldwide [2]. Many Non-Communicable Diseases (NCDs) such as obesity, coronary artery disease, hypertension and diabetes mellitus can be prevented by regular PA. Also, several studies have shown that the aged populations with comorbidities had a higher risk of morbidity and mortality from COVID-19 [3,4]. Physical activity by its ability to boost our immune system can also reduce the burden of communicable diseases [5-7].

Due to the closure of gymnasiums, parks, and fitness centers as well as work from home and the need to wear a mask, there has been a reduction in the levels of physical activity after the onset of the COVID-19 pandemic [8].

Previous studies have shown a disparity between the activity levels in males and females with higher activity levels in males. Several factors contributing to this disparity include limited time availability, insufficient awareness, lack of access to safe roads, unfavorable sociocultural norms, household responsibilities, and inadequate social support and facilities [9–12]. Apart from physical and environmental barriers, psychological barriers have been also shown to play a pivotal role [10].

Although there is considerable knowledge and research concerning barriers to activity, the level of physical inactivity and obesity is on a steep rise. Indicating that the interventions in place do not effectively target the barriers and a failing exists to recognise other factors influencing inactivity.

To effectively reduce the level of inactivity in women we first need to re-examine the burden of physical inactivity

and to determine the barriers to activity. This will further help us in institutionalizing public health policies to combat NCDs.

Thus, this study was taken up with the objectives to assess the physical activity levels in overweight and obese women using WHO global physical activity questionnaire (GPAQ) and to determine the perceived benefits and barriers to exercise using exercise benefits and barrier scale (EBBS).

Material and Methods

This descriptive observational cross-sectional study was initiated after approval from the institutional ethics committee. 96 women in the age group of 18-64 years attending our OPD, health check-ups, and students and staff of our college, who were willing to participate in the study were screened. Those satisfying the inclusion and exclusion criteria underwent a brief clinical examination to rule out any systemic illness. Women belonging to the category of overweight and obese according to the WHO Asian BMI classification i.e. Women whose BMI is between 23-24.9kg/m^2 were considered overweight and BMI greater than 25 kg/m^2 were considered obese were included in the study. Pregnant women and women with disability were excluded from the study. A sample size of 96 was determined at 95% confidence interval using the formula n= z2*p * (1- p) / e2 [12], p-value based on the article [13] and considering allowable error at 10%.

The study procedure was explained to the subjects and an informed written consent was taken.

The height and weight of the subjects were recorded according to the standard protocol. Standing height was measured up to 0.1cm without footwear, with the subjects back to a wall and with both heels placed together and touching the base of the wall. Weight was recorded without footwear, to the nearest of 0.5 kg. BMI was calculated by using the formula weight in Kg / Height in $meter^2$ (Quetelet formula). Body composition was assessed using Omeron Karada scan. The body composition analyzer works on the principle of bioelectrical impedance. Total body fat percentage, fat mass, muscle mass, visceral fat, and basal metabolic rate were derived from it.

The Global Physical Activity Questionnaire (GPAQ) and Exercise Benefits and Barrier scale (EBBS) were administered. The Global Physical Activity Questionnaire (GPAQ), which has been developed by the World Health Organization (WHO) assesses physical activity [14]. This questionnaire has 16 questions arranged in 3 main domains – occupation, travel and leisure activities. GPAQ has been previously validated in Asian Indians and found to be reproducible and reliable. The responses to the frequency and duration questions were used to calculate the total amount of time a person spends doing physical activity or metabolic equivalent (MET) minutes per week.

For adults aged 18–64 years, WHO recommends at least 150 minutes of moderate-intensity physical activity throughout the week, or 75 min of vigorous-intensity physical activity throughout the week; or an equivalent combination of moderate- and vigorous-intensity activity accumulating at least 600 MET-minutes per week [15]. In our study, we have used this cut-off to define physically active versus inactive adults.

The EBBS is designed to determine the perceptions of individuals regarding the

benefits and barriers of participating in exercise. The EBBS is a 43-item rating scale consisting of two subscales, Benefits and Barriers. Ratings are obtained using a four-point response system. The EBBS has been tested for internal consistency, validity of its constructs, and test-retest reliability [16]. Prior permission has been obtained from the author to use the questionnaire.

The Data was collected by conducting interviews with the participants and it was entered in Microsoft Excel sheet and analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, New York, IBM Corp) for statistics. Data was presented as appropriate tables. Mean ± SD for data following normal distribution and median/ interquartile range was used for skewed values. EBBS questionnaire was graded using 4-point Likert's Scale. The mean and standard deviation for each question was calculated.

Results

In this study, we assessed the level of physical activity in overweight and obese women. The demographic characteristics of our study participants have been depicted in Table 1. The level of physical activity has been divided into low, moderate and high, expressed as MET min/week has been depicted in Table 2. The MET min/week attained by the study participants in three domains of physical activity being work, travel and recreation has been expressed in Table 3.

The exercise benefits scale score of the study participants has been expressed in Table 4.

The mean score of the exercise benefit scale and exercise barrier scale questions have been represented in Table 5 and Table 6, respectively.

Table 1. Demographic characters of the study population

Age group 20-30 yrs 31-40yrs Above 40	Frequency 40(41.7%) 20(20.8%) 36(37.5%)
Employment status Student Employed Homemaker	Frequency 17(17.7%) 27(28.12%) 52(54.16%)
Height in m	155.83±6.72*
Weight in kg	66.73±11.05*
BMI in kg/m^2	27.49±3.45*
Fat%	35.55±3.33*
Visceral fat	8.49±3.95*
Muscle fat	23.85±2.40*
Subcutaneous fat	31.45±4.28*
BMR	1360.10±181.76*

*mean±SD

Table 2. Level of physical activity of the study participants (N=96) measured in MET min/week

Levels of Physical Activity	Frequency (percentage)
Low (<600 MET min/week)	33 (34.37%)
Moderate (600-3000 MET min/week)	26 (27.08%)
High (>3000 MET min/week)	37 (38.54%)

Table 3. Mean MET min/week attained by the study participants in three domains of physical activity (work/ travel/recreation)

Activity	Mean± Std. Deviation	Median (25th -75th interquartile range)
Vigorous activity At work	0.00±0.00	0(0-0)
Moderate activity At work	1755.00±3041.63	0(0-2760)
Travel	1374.38±1777.86	660(0-2160)
Vigorous activity At recreation	87.50±398.74	0(0-0)
Moderate activity At recreation	439.79±1065.03	0(0-270)

Table 4. The exercise benefits scale total score of the study participants

	N	Minimum	Maximum	Mean± SD
EBBS total score	96	76	162	110.55± 18.76
BARRIERS score	96	16	51	34.17±6.15
BENEFITS score	96	59	111	76.39±14.07

Table 5. The exercise benefits scale responses of the study participants expressed in frequency (percentage)

	Strongly agree	Agree	Disagree	Strongly disagree	Mean±SD
Physical performance sub-scale					
Question 7	0(0.0%)	47(49.0%)	41(42.7%)	8(8.3%)	2.59±0.64
Question15	0(0.0%)	41(42.7%)	43(44.8%)	12(12.5%)	2.70±0.68
Question17	0(0.0%)	49(51.0%)	39(40.6%)	8(8.3%)	2.57±0.64
Question18	0(0.0%)	31(33%)	47(50%)	16(17%)	2.84±0.69
Question22	1(1.0%)	40(41.7%)	42(43.8%)	13(13.5%)	2.70±0.71
Question23	0(0.0%)	38(39.6%)	46(47.9%)	12(12.5%)	2.73±0.67
Question 31	0(0.0%)	37(38.5%)	49(51%)	10(10.4%)	2.72±0.64
Question 43	0(0.0%)	30(31.3%)	57 (59.4%)	9(9.4%)	2.78±0.60
Life enhancement subscale					
Question 25	0(0.0%)	43(45.3%)	50(52.6%)	2(2.1%)	2.57±0.54
Question26	0(0.0%)	48(50%)	36(37.5%)	12(12.5%)	2.63±0.70
Question 29	2(2.1%)	55(57.3%)	37(38.5%)	2(2.1%)	2.41±0.57
Question32	0(0.0%)	39(40.6%)	48(50%)	9(9.4%)	2.69±0.64
Question34	0(0.0%)	49(51%)	39(40.6%)	8(8.3%)	2.57±0.64
Question35	2(2.1%)	52(54.2%)	36(37.5%)	6(6.3%)	2.48±0.65
Question36	0(0.0%)	53(55.2%)	37(38.5%)	6(6.3%)	2.51±0.62
Question41	0(0.0%)	35(36.5%)	50(52.1%)	11(11.5%)	2.75±0.65
Psychological Outlook Sub-scale					
Question 1	0 (0.0%)	39 (40.6%)	48(50%)	9(9.4%)	2.69±0.64
Question 2	0 (0.0%)	43 (44.8%)	41 (42.7%)	12(12.5%)	2.68±0.69
Question 3	0 (0.0%)	45 (46.9%)	38 (39.6%)	13(13.5%)	2.67±0.71
Question 8	0 (0.0%)	35 (36.5%)	49(51%)	12(12.5%)	2.76±0.66
Question 9	5(5.2%)	40 (41.7%)	44(45.8%)	7(7.3%)	2.55±0.71
Question 20	0 0.0%	37 (38.5%)	48(50%)	11(11.5%)	2.73±0.66
Social Interaction sub-scale					
Question 11	2(2.1%)	66(68.8%)	27 (28.1%)	1(1.0%)	2.28±0.52
Question 30	2(2.1%)	69(71.9%)	21(21.9%)	4(4.2%)	2.28±0.57
Question 38	2(2.1%)	46 (47.9%)	40(41.7%)	8(8.3%)	2.56±0.68
Question 39	1(1%)	60(62.5%)	33 (33.3%)	3(3.1%)	2.39±0.57

Preventive Health sub-scale					
Question 5	1(1.0%)	8(8.3%)	69(71.9%)	18(18.8%)	3.08±0.56
Question 13	0(0.0%)	30 (31.6%)	56(58.8%)	9(9.5%)	2.78±0.60
Question 27	4 (4.2%)	19(19.8%)	66(68.8%)	7(7.3%)	2.79±0.63

Unit: Frequency (percentage)

Table 6. The exercise barriers scale responses of the study participants expressed in frequency (percentage)

	Strongly agree	Agree	Disagree	Strongly Disagree	mean± SD
Exercise Milieu Sub-scale					
Question 9	5(5.2%)	40(41.7%)	44(45.8%)	7(7.3%)	2.55±0.71
Question 12	6(6.3%)	48(50.0%)	37(38.5%)	5(5.2%)	2.43±0.69
Question 14	2(2.1%)	29(30.2%)	55(57.3%)	10(10.4%)	2.76±0.66
Question 16	15(15.6%)	60(62.5%)	20(20.8%)	1(1.0%)	2.07±0.64
Question 28	2 (2.1%)	18(18.8%)	64(66.7%)	12(12.5%)	2.90±0.62
Question 42	5(5.2%)	48(50.0%)	41(42.7%)	2(2.1%)	2.42±0.63
Time Expenditure Sub-scale					
Question 4	8(8.3%)	61(63.5%)	24(25.0%)	3(3.1%)	2.23±0.64
Question 24	5(5.2%)	45(46.9%)	39(40.6%)	7(7.3%)	2.50±0.71
Question 37	4(4.2%)	19(19.8%)	66(68.8%)	7(7.3%)	2.79±0.63
Physical Exertion Sub-scale					
Question 6	4(4.2%)	61(63.5%)	29(30.2%)	2(2.1%)	2.30±0.58
Question 19	6(6.3%)	37(38.5%)	52(54.2%)	1(1.0%)	2.50±0.63
Question 40	7(7.3%)	56(58.3%)	31(32.2%)	2(2.1%)	2.29±0.63
Family Discouragement Sub-scale					
Question 21	3(4.2%)	29(40.8%)	31(43.7%)	8(11.3%)	2.62±0.74
Question 33	2(2.1%)	31(32.3%)	46(47.9%)	1717.7(%)	2.81±0.74

Discussion

This study aimed to determine the level of physical activity and the perceived benefits and barriers to exercise in overweight and obese women. The mean BMI of our study participants was 27.49±3.45kg/m^2, 54.16% of them were homemakers (Table 1). We found that 34.3% of the participants were physically inactive, 27.08% were moderately active, and 38.5% were highly active based on their MET scoring on the GPAQ questionnaire (Table 2).

A study done in India, found the prevalence of self-reported physical inactivity among adults to be 52.1% [17], other Indian studies have found the level of inactivity to be 56.8% [18] and 49.7% [19]. The level of physical activity in these studies was much lower as compared to our study. This difference could be attributed to the fact that a large percentage (54.16%) of our study population were homemakers, who performed daily household chores adding to their levels of physical activity. As depicted in Table 3 moderate activity at work contributed to a significant portion of MET min/week followed by activity involving travel to and from work place. However, MET min/week spent on recreational activities was found to be low. This information can help initiate programs that will focus on increasing time spent on recreational activities.

The study also aimed to understand the perceived benefits and barriers to physical activity in our participants. For this, we utilised the Exercise benefit and barrier scale which is a four-response, Likert-type format with responses ranging from 4 (strongly agree) to 1 (strongly disagree). Barrier Scale items are reverse-scored. The total instrument scores can vary from 43 to 172, with higher scores indicating a more positive perception of exercise. When the Benefits Scale is used independently, scores range from 29 to 116. The total score obtained in our study was 110.55±18.767 (Table 4) indicating that the participants perceived exercise positively.

In the benefits scale, under the domain of physical performance subscale, it was observed that Question 18 'Exercising improves the functioning of my cardiovascular system' was the most agreed benefit with a mean score of 2.84±0.69, this could be because of increased awareness among the general population about the cardiovascular problems and the positive influence of exercise on the health and how it can prevent coronary artery disease and mortality. Under the domain Life Enhancement Sub-Scale Question 41 'Exercise improves overall body functioning for me' was the most agreed upon with a mean score of 2.75±0.65. In the domain Psychological Outlook Sub-scale, Question 8 'Exercise gives me a sense of personal accomplishment.' was mostly agreed upon with a mean score of 2.76±0.66.

Physical activity is known to act as an adjunct for alcoholism and de-addiction programs, helping in improving self-image, social skills, and cognitive functioning, also to reduce episodes of anxiety [20].

Under the domain of social interaction subscale Question 38 'Exercise is good entertainment for me', a mean score of 2.56±0.68 was obtained. The perception of exercise as a form of entertainment rather than a chore or punishment will help to improve adherence to exercise in the long term.

The responses to the barrier scale were reverse-scored, with a low score indicating that the participant was in agreement with the statement. The lowest

score was obtained for question 16 which stated 'Exercise facilities do not have convenient schedules for me'. Indicating a time restraint to perform exercise. Other questions with low scores were, 'Exercising takes too much of my time', 'Exercise tires me', and 'Exercise is hard work for me'. All these indicate that paucity of time is one of the major barriers to performing exercise along with personal limitations to perform exercise.

Under the domain of exercise milieu sub-scale Question 28: 'I think people in exercise clothes look funny.' was mostly disagreed upon by the study population. It can be explained that the general public is now aware of the pros of using sportswear, and that wearing them is not funny anymore but rather fancier.

It was found in the present study that 51%of the women did not have access to public exercising areas such as gymnasiums and parks which may have attributed to decreased levels of recreational-based physical activity in these women.

Another observation in the study was that 58.3% of the highly active group had an EBBS SCORE of more than 110.55± 18.767, whereas 69.69%of the inactive group had an EBBS SCORE of less than 110.55± 18.767, this can be interpreted as, people with high physical activity perceive comparatively fewer barriers, whereas the inactive group perceive a lot of barriers for exercising.

Conclusion

In conclusion, physical inactivity among overweight and obese women was found to be at 34.3%. Time spent on household chores and workplace attributed to most of the physical activity performed. Lack of time and personal fatigue was cited as being one of the major limiting factors to performing exercise.

Interventions that make it convenient to exercise, as well as strategies that target the way exercise is perceived by the population, need to be initiated to help increase the levels of physical activity and decrease the mortality and morbidity due to lifestyle-related disorders.

Limitation

The limitations of our study are a relatively small sample size and involving subjects from the hospital and college, so the results cannot be generalized to the general population.

Acknowledgment

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Conflicts of interest

The authors declares that they do not have conflict of interest.

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REVIEW ARTICLE

How to Perform a Postgraduate Research and Write a Scientific Paper: The Underpinning Facts!

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Abstract

This article is a narrative review that focuses on the common shortcomings that one researcher faces. The aim of the article is to provide some key ideas to the novice researcher how to overcome those hurdles. The electronic database such as PubMed, Google Scholars, Science Direct, ProQuest are searched to find the related articles. Only the full text articles were considered. Mostly, the consensus views are presented in most of the topics. Some of the gray zones are discussed. The article will help the aspirant author to complete their research and academic writing in a presentable manner.

Keywords: Research Design, Outcome Assessment, Health Care, Sample Size, Random Allocation, Selection Bias

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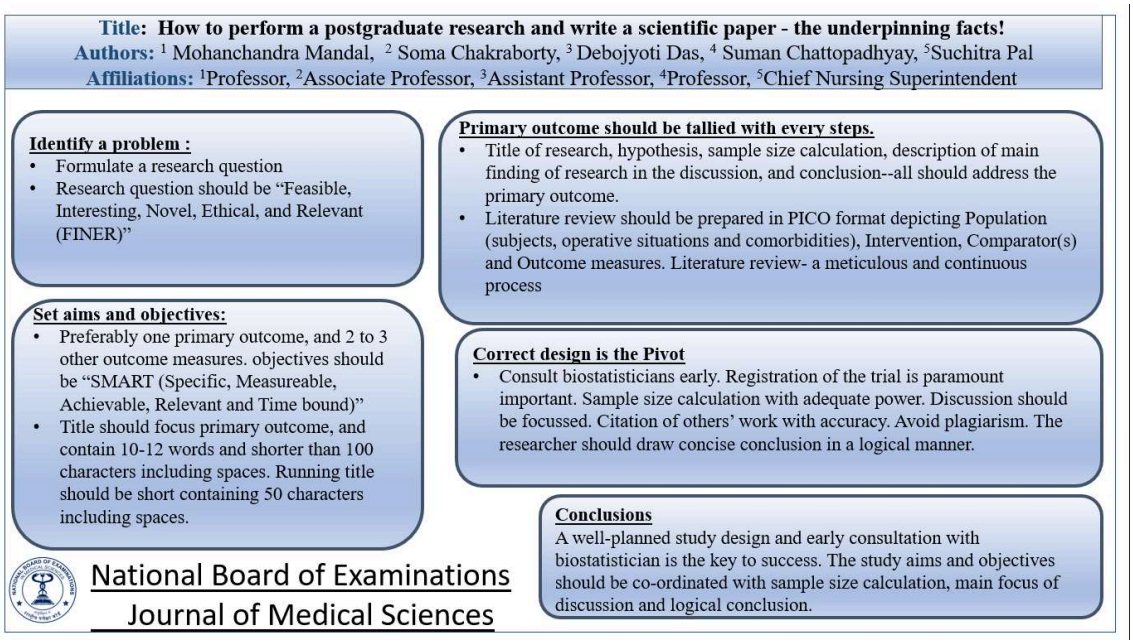
Graphical Abstract



Introduction

A thesis or dissertation is an academic document that presents the author's research findings to answer one or more research question(s) [1]. Thesis and dissertation are some commonly used terminologies in the sphere of academy and research. Although, used interchangeably, they may have different meaning and implications that varies with countries and institutes [2]. Usually they differ in academic level and regarding the scope and depth. What's in a name! Whether it is a thesis or a dissertation, both need the same seriousness. Both require critical thinking and some basic rules such as time management, continuous literature search, improved writing, and attaining other soft skills.

Often the researcher feels pressure to complete their research works and consider the task of writing a thesis as potentially intimidating and boring [1]. However, they should follow some general principles that will make this apparently hard process enjoyable. Planning and writing the thesis in an organised manner should be the goal. Some important points to be remembered during conduct of a research (Figure 1).

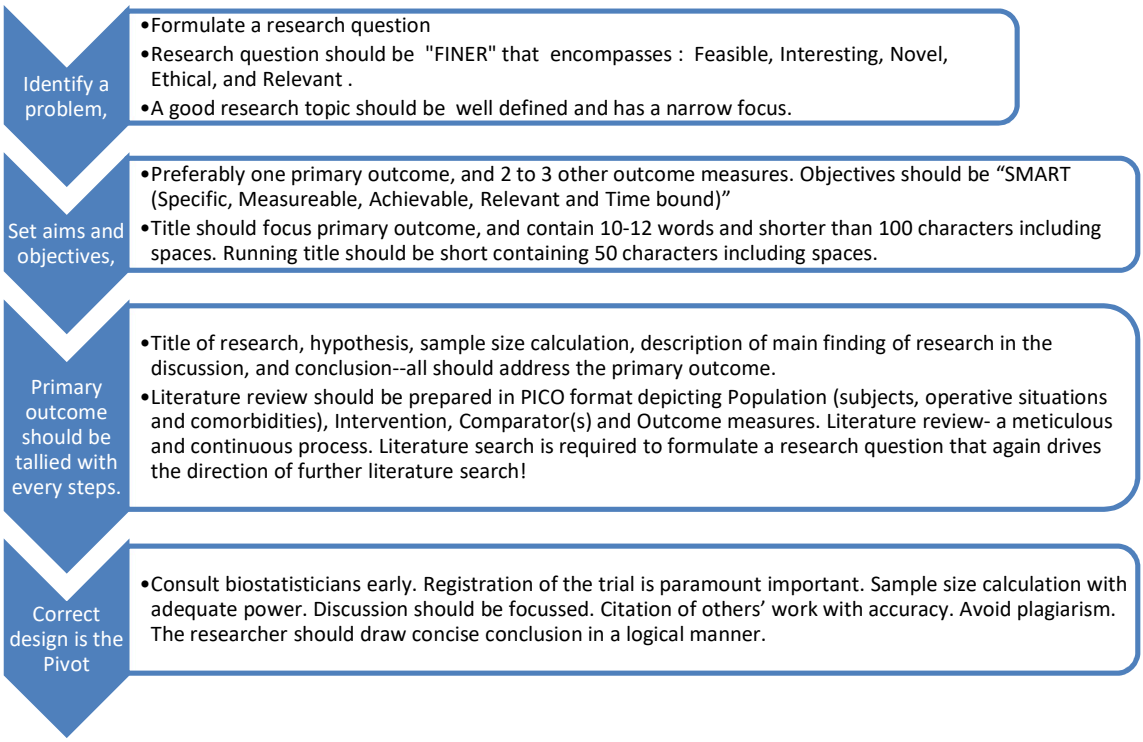


Figure 1. Important points for conducting a research.

Review

Formulating research question is the key element

After getting induction into which topic one will do the research, the candidate should consult guide(s) to formulate the research question first. The investigator should assess whether the research question is "Feasible, Interesting, Novel, Ethical, and Relevant (FINER)" before starting the research [3,4]. Although we are talking about the novelty, the research question need not to be entirely original. The researcher should do an exhaustive literature review on the related topic at first. It is helpful if a broad sheet (tabular information sheet) is prepared in PICO format depicting **P**opulation (including different operative situations and comorbid conditions of subjects) under the study, **I**ntervention done, **C**omparator(s) used in that study, and **O**utcome of the intervention [5]. Thereafter, on careful observation of the broad sheet, the researcher will be able to detect some lacunae in the existing field of research regarding the following aspects. Investigator should try to detect any special subset of population, any variety of intervention or a different outcome that remained not studied. These are the areas where we can try some other new. Observe carefully about what outcome has already been studied and we can do study on any other aspect. This small change will make the study a bit new. It will address the lacunae in the existing literature that is an important point of adjudication of the introduction section of thesis. Overall, on careful observation of such a broad sheet the investigator will be able to prepare the justification about why this can be an interesting topic to do a research. A good research topic should be one that is well defined and has a narrow focus [6]. A properly framed research question makes

the backbone of a research [6]. Research question relates with hypothesis intimately with a subtle difference between the two. Research question indicates about the idea under study while the hypothesis framed aims to answer the research question. The research question can be converted into a hypothesis by converting it into a statement [7].

It is crucial to set the primary objective of the study based on the study hypothesis and secondary objectives based on other relevant research questions of interest [4]. The study objectives should be "SMART (Specific, Measureable, Achievable, Relevant and Time bound)" to be effective research parameters [4]. Aim of a study describes the broad areas of the research encompassing the research objectives [8].

The researcher should compose a title containing the theme of primary outcome and address all facets as per PICO format. The title appears as the 'first detail' or 'face' of a thesis or paper that one reader look upon. Hence, it should contain 'just enough details' to kindle the interest among the reader [9]. Lengthy titles can appear boring, clumsy, unfocused and will not transmit proper information to the readers. Initially one can go with a working title. Authors should draft the title to make it accurate, and precise. The recommended word limit of the title varies in the literature and is a gray zone. As a rule of thumb, the ideal length of a title is 10-12 words and shorter than 100 characters including spaces [10,11]. According to other literature, the word count of title should not exceed 12-16 words or the limit of 150 characters [12]. Although some authors [13] opines that title should accommodate as many words as necessary to explain the main theme of the research without much emphasis on the length, an editor's perspective [14] guides that a "good title should not contain more than 15 words or 100 characters".

Correct design is the Pivot

The study design should be appropriate, rigorous, and comprehensive. The researchers should design the study correctly and for that, they must have a comprehensive knowledge on the basic structure of study designs [15]. Often, a thesis mention in the title or in the methods section that it is an observational study while later it is seen in the details of methodology that the researcher has actually assigned the participants in some way that means it is a true experimental (interventional) design indeed. In descriptive study, the investigator tries to describe the characteristics of a sample population. In analytical study, the researchers attempt to analyse and draw inferences about any relationship between the variables. The analytical study again can be experimental or observational. In clinical trials (true experimental study/ interventional study), the researcher intervenes with something either to prevent a disease or to treat it. Here the researcher will actively assign the participants to receive that intervention. In contrast, the investigator makes no active intervention in observational studies; rather take a note about the patients receiving the treatment based on clinical decisions. For example, if investigator wishes to determine the prevalence of hypothyroid diseases, diabetes, ischaemic heart diseases or hypertension among the patients attending the preoperative clinic of this hospital for one year- it may be an observational study. Another example,

when the investigator wishes to find the incidence of post-dural puncture headache (PDPH) among patients receiving spinal anesthesia with different gauze needle and he is not assigning the needle gauze for any particular patients, it becomes an observational study. Here, the patients are receiving the therapy according to the preference of the conducting anesthesiologist and the investigator is just observing the incidence of the PDPH. The detailed description of study designs is out of scope for discussion in this article. Interested reader can consult the referenced resources [16,17].

Nowadays, the researchers often perform "qualitative research" to understand human experience, behavior, and perception. Qualitative research focuses into real-world problems to explore deeper insights instead of acquiring numerical data. Here, the researcher tries to organize recurring themes in the data (thematic analysis) by observation or interacting with a focused group. The researcher can use delve research hypothesis for further quantitative study. Delve is qualitative coding software that is used to analyse qualitative data. Delve provides an intuitive interface and artificial intelligence (AI)-assisted features that can be used by the researcher as assistant [18]. This simple tool ensures collaborative online qualitative analysis to find rigorous, human insights quickly. Delve provides a seamless organization and powerful analysis of qualitative data with human touch to derive proper conclusion(s). AI appears to be a powerful tool for analyzing data. However, it may not be able to construct the meaning that a human researcher can do [18].

Other areas of study include the delivery of healthcare, prognostic/diagnostic research, medical education technique etc. A new concept gaining appreciation is the close bidirectional flow of knowledge between basic, clinical and community research and translation of this knowledge in generation of further research [19].

In case of experimental study, the researcher forms one hypothesis at the end of the introduction. The hypothesis tell clearly, what is being expected from the study. First, the researcher assumes that there is no difference in outcome with application of either of the interventions and the study result will disprove or reject that. It is termed as null hypothesis. One can formulate the alternative hypothesis that directly states what the probable outcome of the study is.

Consult biostatisticians early

It is quite important to keep required raw data what is necessary for testing and analysing the outcome. If we miss to record any important data and the study is completed, it is totally undone. No statistician can help us out. It is utmost important to keep data in a proper format and analysing them using correct statistical methods. If the necessary raw data is there, re-analysis can bring the important conclusion from that data. Hence, it is important to take the advice of the biostatistician at the very beginning about observable parameters and their format. It is better to consult a statistician at different phases of the study such as, designing the study, before and after data collection, during data analysis and logical conclusion. In the methods section, the researcher should mention details about data collection- how, when, how often, where and who collected data, how the data collector remained blind,

randomization, etc. It is important to describe how the raw data was processed and analysed. It is better to avoid simple listing of series of tests. Instead, try to mention the specific tests used to analyse each type of data. After completion of data analysis, describe the result with appropriate writing in the text form [20].

Literature review- a meticulous and continuous process

The literature review process is a paradox. Literature search is required to formulate a research question, which again drives the direction of literature search. The methodology is prepared based on research question and literature. The review and research question(s) helps the researcher to have an idea about data collection and analysis. The complexity of the research question warrants the intensity and ramification of the literature review [21]. Often a particular methodology for a study selected in such a way that it would contribute to expand the knowledge beyond what published previously in the related topic. Even for a simple research question, there is need for further search on the topic.

The researcher cannot effectively carry out a literature search without formulating the research question(s). On the other hand, the literature review can play a vital role in formulating the problem statement in to an effective research question(s). It will help constructing a summary on existing knowledge about the topic. Thus, it would throw light on the lacunae in the existing literature where the investigator would focus. It will certainly make the study novel and will contribute something new to the related field. The literature review helps to acquire a detailed understanding of the topic. It also helps to conceptualise the research question precisely and makes it more relevant in the field of investigation [22]. The literature review is started from the beginning of the study, and should be continued till final writing of the thesis to include the latest researches in the discussion of context. At time of final submission of thesis the literature review is summarized in any of three ways – systemic (generation and comparison of evidence as per theme), semi-systemic (tracking evidence in time) or integrative (qualitative evaluation as a critique) [23].

Systematic reviews is performed when researchers have a more precise or specific research question addressing the feasibility, appropriateness, or effectiveness of a particular treatment or practice [24]. A strict search strategy is followed to select articles to be included in the review. This review is effective in synthesizing what the included studies are showing evidence on a particular question [23]. *Semi-systematic review* is conducted when there is a broad research question and the researchers wish to study a broader topic. The purpose is to overview research area and track development over time. The search strategy may or may not be as stringent as systematic. A semi-systematic review approach could be a good strategy to identify knowledge gaps within the literature and to map theoretical approaches or themes [23]. *Integrative review* can be useful when the research question requires to be a more creative collection of data. It provides a comprehensive understanding of a phenomenon from a synthesis of all forms of available evidence [25]. Here, the research question can be narrow or broad. The purpose of the review is not to cover all articles ever published on the topic.

Instead, it tries to combine perspectives to create new theoretical models. Integrative review considers diverse study designs such as experimental, non-experimental, quantitative as well as qualitative researches to reach its conclusions. Integrative reviews warrants specific skills to identify and synthesise literature [26]. A detailed insight into the most common types of review is available in the literature [27].

Materials and Methods

The methods section should be flawless and contain detail information for replication of the study successfully. Here, the investigator should mention the details of population- how they are selecting patients, inclusion and exclusion criteria, trial registration, Institutional Ethical Committee (IEC) permission and written informed consent. The investigator should mention where the work is done, the speciality of the operating room (OR), for example, general surgery, gynaecological OR, etc. instead of the specific name of that OR as given by the institute.

Registration of the trial is paramount important

Wilful concealment of results and lack of transparency in reporting of data can degrade the quality of evidences in the medical practice. It is ethical and moral responsibility of the researcher to register the clinical study protocol in the trial registry such as International Clinical Trials Registry Platform (ICTRP) or Clinical Trial Registry of India (CTRI). The WHO Registry Network is composed of Primary Registries or Partner Registries. Some registries are working with the ICTRP towards becoming Primary Registries. Researchers can access the ICTRP search portal (https://trialsearch.who.int) or other registries (such as https://clinicaltrials.gov/), in the ICTRP Network. The researchers can try for Universal Trial Number (UTN) at https://trialsearch.who.int/utn.aspx that will help uniquely to identify clinical trials registered in WHO Primary Registries. They provide facilities to register trials in prospective manner. The trial registries work together as a forum to exchange information and help to establish the best practice for clinical trial registration [28].

Sample size calculation with adequate power

Researcher should mention sample size in the methods section. While writing text on sample size, the investigator should be careful about mentioning all necessary components such as power, alpha error, effect size and standard deviation or proportions of any referenced article. In most of the cases, there is mention about power and alpha error. However, the investigator should mention the effect size also. *Effect size* is the 'minimum clinically important difference' between the groups that the investigator wishes to detect [29]. This effect size should be set on the basis of *primary outcome* measure. Investigator assumes this, and thereby there is some scope of flexibility. However, this assumption should be clinically relevant and thus has some bindings as well. When evaluating a drug's effect on heart rate, an effect size of 10 beats per minute can be clinically relevant. In contrast, when we evaluate a new analgesic agent on postoperative analgesia an assumption of 10 minutes difference regarding the time to receive first rescue analgesia may not be useful clinically. The researcher should

furnish one reference against the data taken from the previous study used for sample size calculation. Besides, the researcher should furnish a reference for the formula or method used for calculation of the sample size. These are to provide the reader a scope to have an in-depth reading and understanding the matter [30]. In case where no previous data exist, the researcher should carry out a pilot study with recruitment of 10-30 subjects or 10% of sample size [31].

Randomisation and allocation concealment in Experimental study

In case of true experimental study, researcher should properly mention about randomisation, allocation concealment and blinding. *Randomisation* is a method that provides 'every subject an equal chance' to be assigned to any group. Random allocation is a process that allows choosing of participants for intervention and comparator groups entirely by chance without addressing the patients' condition, and the will or preference of researchers. This process permits mitigating the influence of all unknown as well as known factors that might influence the outcomes in both the treatment and control groups [32]. This random allocation process consists of two steps: (i) yielding an random or unpredictable sequence of intervention (*randomisation*), (ii) implementing the sequence to conceal the treatments (*allocation concealment*) until participants have been formally assigned to the respective groups.

Blinding is a technique that tries to keep the participants, the researcher or both to be unaware of the assigned intervention [32,33]. The study is single-blind when only the participants are blinded. In a double-blind study, participants and researchers- both are blinded. In a triple-blind study, the intervention is kept hidden to not only the participants and researchers, but also to the researchers who are analysing the data. This will help reducing selection bias, implementation or performance bias and measurement bias [4]. This is to prevent bias of the investigator and team members to allocate the preferred intervention to selected participants to generate a favourable outcome of interest. The use of sequentially numbered, opaque, sealed envelopes can be one such technique [4].

The investigator should mention the details of methodology so that a reader can replicate the study with ease. There should not be any difficulty in understanding the flow of the process [34,35]. The researcher should provide the adequate definition of every measured variable. There should be adequate definition of adverse events and management. Whenever a specific score, scale or grade is being used the researcher should provide a brief description with reference.

It is important to narrow down research from a myriad of sources (Google Scholar, PubMed, Embase, Medline etc.) by using suitable search engine with appropriate keywords, Boolean operators and other search limiters as applicable so that the researcher does not lose the way [36]. However, cross-referencing of important cited articles and limitation is also important.

Results Section

The results section may begin with a short description of the study type and the time span of the study. Near the end of methods section or in the beginning of results section, the researcher should place

a flow chart that will give the reader an idea about the basic structure of the study design, number of drop out and any lost to follow up [37].

For proper analysis, the researcher should have a comprehensive knowledge about the types of data and the suitability of tests to analyse those [4,38-40]. It is important to present data in a comprehensive and palatable format. When the categorical data (e.g. ASA physical status classification, gender) are analysed by using Chi-square test it is better to use the Chi-square value and *P* value rather than the mere copy pasting of statistician's analysed data en masse which bears unnecessary numerical jugglery with individual row, column and total proportions. The latter can camouflage the necessary information and the reader face difficulties in focussing. It would be easier for the readers to grasp the essence of the presented data if the table is neat and clean by avoiding unnecessary numbers after decimal. It is practically useless to write mean and standard deviation (SD) of heart rate as 89.461±10.292 and therefore can be simplified as 89.5±10.3 without any harm. Although this simplified presentation of data is practical with ease of reading and appreciation in case of large sample, providing data up to second decimal would bear importance if the sample size is small. It is important to clean and cross check data and statistical analysis.

Another aspect while describing the result one should avoid writing mean and SD including the *P* values in the text. Instead of repetition of such data, the investigator should cite the table number or figure number to refer the reader to the particular table or figure and describe the essence of the displayed data what that actually indicates. However, some researchers prefer to highlight the primary and secondary study objectives in both table and figure.

When presenting the results, one can mention the point estimate along with the 95% confidence intervals, which convey much more than just the *P* value [41]. Use of confidence intervals and interpreting it in a proper way can be more informative than mentioning the *P* values. The researchers should be well conversant with the use of confidence intervals.

In the results section, try to avoid use of simultaneous tables and figures for variables that are not any outcome measures of interest. Tables should preferably be used for furnishing detailed information with sizeable data that may be useful to compare [35,42]. In contrast, the patterns or trend are better expressed using figures [35,42]. The investigator can use both table and figure formats simultaneously to present the most important observations i.e., the findings on the primary outcome to create impact among readers [43].

During final writing of the thesis, often the researcher copies the methodology from synopsis and forgets to alter the future tense of the sentence to past tense. It is paramount important to maintain the spelling of any particular format - either United Kingdom or United States of American style.

Discussion should be focussed

In the initial phase of discussion, the researcher should depict the main observation of the study, the *primary outcome* [44]. The researcher should attempt here to answer the research question(s) with an explanation how the observed results fit with the current literature, with critical analysis and

shortcomings of the existing knowledge [35,45]. Ahmad [46] described it as the 'liveliest part' of a research. The main goal of discussion is to think critically about the work by framing a constructive debate with literature support. Agreement and disagreement with the present study findings can better be resolved if one thinks about the possible improvements under what conditions previous authors had achieved that results [46].

Researchers should avoid repetition of numerical details of data (mean ± SD with *P* value). Instead, they can provide the magnitude of benefit achieved with the new intervention using plain language summary. A detailed numerical value with values many places after the decimal are useless. Rather, a rounded off value offers the benefit of easy readability owing to simpler in text appearance and serves the purpose of clinical utility.

After mentioning the main observation of the present study, furnish the findings of different studies in the related field. It would be prudent to corroborate or contrast the present study findings with others' work in the related field. The researcher should take precaution during selecting the number of *secondary outcomes* while designing the study during synopsis protocol. It is safer to keep not more than two to three secondary outcomes. It would be uncomfortable to cover the discussion on too many secondary outcome measures and to extract the essence to draw conclusion. It is important to check that the objectives of the study are identified at Introduction, followed up in review of literature, appropriately researched and analysed and finally discussed. An argument matrix is a checklist tool so that any vital information may not be missed [47].

Often the researcher mention the result of other studies as mean ± SD with *P* values with specific group names of that particular study. It would be easier for the readers to grasp the information if the researchers state the magnitude of difference achieved and avoid SD and *P* values as far as practicable. The researcher should state whether it is 'comparable' or there is 'considerable difference' to indicate the non-significant and significant values.

Citation of others' work with accuracy

While stating other authors' works, furnish it with appropriate reference. Avoid using copy pasting verbatim. Instead, use your own words keeping the scientific meaning unaltered. We should check all texts using plagiarism checker available online. Last but not the least, the references should be written in the proper format as per the university rules. The researcher should follow only one format-the National Library of Medicine (NLM), the American Psychological Association (APA) or any other, throughout writing of one research work. The whole file should be stored in different devices and in the clouds if feasible, to protect against loss. The files should be stored after renaming it properly (can use date) to avoid any confusion with older version. Several organizations such as 'International Committee of Medical Journals Editors (ICMJE)', 'World Association of Medical Editors (WAME)' and 'Committee on Publication Ethics (COPE)' provide publication ethics, various recommendations and guidelines to assist authors, reviewers and editors. These are helpful to prepare and disseminate

unbiased and reproducible research papers [48]. The aspirant researcher should consult those. In case of voluminous collection of references the tools such as Zotero, Mendeley, EndNote etc. can be helpful [49]. The important steps of research are summarized in Box 1.

Box 1: Key points to be followed during research

- Identify a problem, formulate a research question
- Research question should be "Feasible, Interesting, Novel, Ethical, and Relevant (FINER)"
- Set aims and objectives, preferably one primary outcome, and 2 to 3 other outcome measures.
- Avoid selecting too many secondary outcomes. It is better not to keep more than two to three secondary outcomes otherwise discussion would be lengthier, the focus would be diluted, and there will be difficulty to extract the essence to draw conclusion.
- Objectives should be "SMART (Specific, Measureable, Achievable, Relevant and Time bound)"
- Title should focus primary outcome. Title should preferably contain 10-12 words and be shorter than 100 characters including spaces.
- Running title should be short and contain 50 characters including spaces.
- Title of research, hypothesis, sample size calculation, depicting main outcome of research in the discussion section, and drawing conclusion--all should address the primary outcome.
- Literature review should be prepared in PICO format depicting Population (subjects, operative situations and comorbidities), Intervention, Comparator(s) and Outcome measures.
- Literature review- a meticulous and continuous process. Literature search is required to formulate a research question, which again drives the direction of literature search.
- Correct design is the Pivot. Sample size calculation with adequate power. Consult biostatisticians early.
- Registration of the trial is paramount important.
- Discussion should be focused. At the outset of discussion, the researcher should depict the main observation of the study, and then try to corroborate or contrast with others' works.
- Citation of others' work with accuracy. Avoid plagiarism.
- The researcher should draw concise conclusion in a logical manner.

Limitations of the study

There should be a subsection regarding the limitations of the study at the end of discussion. Here, mention the pitfalls of the study. Do not mention or elaborate on exclusion criteria of your research. The basic idea is to look into the study retrospectively in terms of study design, resources, access to studies, population chosen, etc. and to look at scopes for improvement [50-52]. The investigator can mention a few words on future scope of the study to address these issues.

Conclusion section

The researcher should draw concise conclusion in a logical manner. The conclusion should state the inference on the primary outcome or main theme in a clear but concise manner. The conclusion should be logical that means it is drawn based only on the specific observations and their significance. The investigator should focus on the objectives and hypothesis of the study once again during drawing conclusion [53]. The conclusion must be explicit whether the observed outcome affirm or negate the research hypothesis [54]. Important findings of secondary objectives should also be mentioned in conclusion.

A final word is to organize your thesis into appropriate sections including relevant accessory materials like certificate from guide and head of institution, ethical clearance, trial registry, university registration, case record form, informed consent form, master chart, and list of tables, figures and abbreviations, plagiarism check report, Gnatt chart of study timeline and acknowledgement of funding sources and conflict of interest. Various checklists are also available at the 'EQUATOR Network (Enhancing the QUAlity and Transparency Of health Research)' available at: https://www.equator-network.org/. The authors should check suitable one based on their study design.

Conclusion

A well-planned study design and early consultation with biostatistician is the key to success. The study aims and objectives should be co-ordinated with sample size calculation, main focus of discussion and logical conclusion.

Declaration

An abridged version on the topic entitled "How to write the postgraduate thesis- the secrets unveiled" has been published in the souvenir of the Joint Annual Conference of Anaesthesiology, Critical Care and Pain Medicine, 2023, organized by ISA Tripura State Branch, held on 10th September at IMA House, Agartala. Subsequently, the text extended to cover other aspects. This article sufficiently distinct from the text of aforementioned souvenir is submitted to this esteemed journal for wide dissemination of current information to a greater number of readers.

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Conflict of Interest

The authors declares that they do not have conflict of interest.

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REVIEW ARTICLE

The Impact of Sugar-Sweetened Beverage Taxes on Dental Well-being

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Abstract:
The World Health Organization (WHO) considered it as an effective strategy to reduce sugar consumption. The gradual intake of sugar-sweetened beverages (SSBs) has a significant public health concern, in relation to dental caries, obesity, and other non-communicable diseases (NCDs). Many countries have implemented taxes on sugar-sweetened beverages to reduce their consumption. This review deals with the dual benefits of sugar-sweetened beverages taxes one is by reducing the prevalence of dental diseases and the second by generating revenue for public health initiatives. Certain case studies from countries like Mexico, India, and UK, have shown positive impact of sugar-sweetened beverages taxes on both oral health and economic sustainability. There are some challenges like potential regressive effects and industry opposition, and some of the evidence has shown sugar-sweetened beverages taxes can greatly reduce sugar consumption, enhance public health outcomes, and decline healthcare costs. A few recommendations like allocating tax revenue to oral health education, implementing graduated tax rates based on sugar content, and launching awareness campaigns can help in improving the oral health status of the population. Globally, sugar-sweetened beverages taxes play a promising public health strategy to overcome the rising burden of oral diseases as well as other non-communicable diseases.

Keywords: Sugar-Sweetened Beverages, Dental Caries, Oral Health, Public Health

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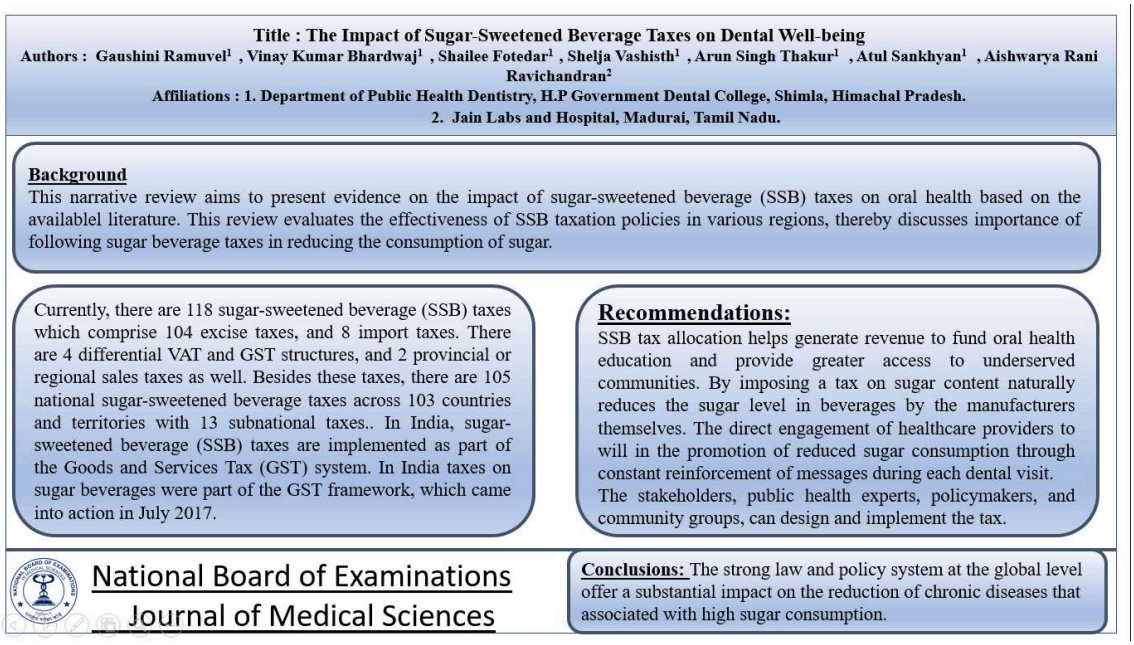
Graphical Abstract



Introduction

Sugar plays a major role in causing tooth decay, and it is necessary to reduce sugar intake in order to decrease the risk of cavities [1]. As a public health measure taxing sugar-sweetened beverages (SSBs) came into play which aimed to reduce the consumption of sugary drinks, which are a major concern towards dental caries and other health issues [2]. Sugar-sweetened beverages (SSBs) contain greater amount of added sugar. Drinks such as sodas, fruit, energy, sports, sweetened teas, and other beverages often contain added sugars. The greater amount of sugar content in these beverages influences significantly daily sugar intake leaving the individual at greater risk of exceeding daily recommended limits [3].

The World Health Organization (WHO) recognized that sugar-sweetened beverages are responsible for non-communicable diseases (NCDs) such as obesity, type 2 diabetes, and cardiovascular diseases [4]. The WHO has given a recommendation on sugar-sweetened beverage taxes which suggests that by increasing the cost of sugar sweetened beverages, it will lead to reduction in the purchase and decreases its consumption. The ultimate aim is to make sugar-sweetened beverages less affordable and encourage each individual to make healthier choices followed by improving overall health outcomes [5]. The role of dietary carbohydrates is to initiate and progress the dental caries. Caries are found to have a stronger association with the frequency of sugar intake than the amount of sugar ingestion [6]. The Australian Institute of Health and Welfare (AIHW) reported that children aged between 2 and 3 years receive 8% of their daily energy intake from free sugars. Recently it was seen that the majority of this sugar intake is dealt with sugar-sweetened beverages [7]. It is evident that there is a linear dose-response relationship between sugar and dental caries, and the World Health Organization (WHO) has recommended the reduction of free sugar intake up to <5% of the total energy intake. Approximately 25 g

of sugar and 20 g of sugar can be consumed by an adult and children respectively [4].

The consumption of sugar-sweetened beverages (SSBs) has become a major public health concern due to its direct impact on various health issues, like dental caries and non-communicable diseases (NCDs) like obesity, diabetes, and cardiovascular disease. The global market is fully loaded with sugary drinks which greatly impact one's oral and overall health. Due to this many countries have given fiscal policies, specifically dealing with taxes on SSBs, as it acts as a strategic approach to decreasing the consumption of sugar-sweetened beverages and helps in reducing the health risks.

Taxing sugar-sweetened beverages not only helps to reduce the prevalence of dental diseases but also greatly acts as an economic tool to influence consumer behavior. It will help them by providing long-term health benefits. The revenues generated from these taxes can be used wisely in public health initiatives which will further enhance positive impact on both general and oral health. This review provides insight into the dual benefits of sugar-sweetened beverage taxes by examining both the economic advantages and its role in improving dental health. The existing literature has shown how sugar-sweetened beverage taxes can act as a powerful instrument in fighting against noncommunicable diseases.

There is a variety of approaches to implementing sugar-sweetened beverage taxes in order to bring changes in the consumer's behavior towards their oral health needs. Currently, there are 118 sugar-sweetened beverage (SSB) taxes which comprise 104 excise taxes, and 8 import taxes. There are 4 differential VAT and GST structures, and 2 provincial or regional sales taxes as well. Besides these taxes, there are 105 national sugar-sweetened beverage taxes across 103 countries and territories with 13 subnational taxes. Due to public health concerns, there is a global commitment to implement sugar-sweetened beverage taxes to curb the consumption of sugary drinks [8]. In the year 2016, the WHO initiated the taxing law by increasing the tax on sugary drinks by 20% as a strategy to decrease sugar consumption [1]. Over 57% of excise taxes on sugar-sweetened beverages are specific taxes, which means they are levied as fixed amounts based on measurements in liters or grams of sugar consumption. Ad valorem taxes comprise 35% which deals with a percentage of the product's value. The remaining 9% are mixed taxes [8].

The majority of the excise taxing systems are seen in North America, Europe, and Central Asia, followed by East Asia the Pacific, and South Asia. Middle East and North Africa, Latin America and the Caribbean, and sub-Saharan Africa follow an Ad valorem taxing policy. High-income countries use specific taxes, while low- and middle-income countries mostly use ad valorem or mixed taxes. There are only three countries like Cook Islands, Mauritius, and South Africa which follow purely sugar-specific excise taxes. Both Poland and Sri Lanka use sugar- and volume-specific taxes. Ecuador's mixed taxing system is a combination of ad valorem and sugar-specific components which deals with applying different costs based on sugar content and product type concerned.

Taxation policy

In **North America**, Mexico introduced a tax of 1 peso per liter on SSBs in 2014, reducing consumption [9,10].

South American countries include Ecuador, which implemented a 0.18 USD per liter tax in 2016, and Chile, which imposed an 18% tax on sugary drinks in 2014 [11,12]. Brazil has some state-level taxes but lacks a national policy, while Colombia proposed a tax in 2016, with some local jurisdictions adopting similar measures [13,14]. In **Australia, a** 20% SSB tax was implemented and it was found that there was a reduction in tooth decay and also saved the cost in dental care [15]. In **Europe**, Estonia introduced a tiered tax on sugary drinks based on sugar content in 2018. Norway increased existing taxes on sugary products, including beverages. Hungary's "public health product tax," effective since 2011, covers sugary drinks [16]. France established a tax on sugary beverages in 2012, later adjusting it to include artificial sweeteners [17]. Finland's tax, effective since 2011, varies by product, and Romania proposed a sugar tax in 2019 [18]. Ireland launched a sugar tax in 2018, with rates depending on sugar content, while Portugal and Belgium also introduced taxes on sugary drinks [19].

Middle Eastern countries with SSB taxes include Egypt, which implemented a tax in 2016, Saudi Arabia, which introduced a 50% tax on sugary drinks and a 100% tax on energy drinks in 2017, and the UAE, which also imposed a 50% tax on sugary drinks and a 100% tax on energy drinks in 2017 [20]. Concerning **Asia**, ever since 2017 India has followed a 28% Goods and Services Tax on sugary drinks [21]. In the year 2017, Thailand implemented a sugar tax by increasing costs based on sugar content [22]. The Philippines also introduced a sugar-sweetened beverage tax in 2018, by imposing varied rates on sugary drinks based on their caloric and non-caloric sweeteners [23]. In Sri Lanka, the sugar-sweetened beverage taxes were introduced in 2017 by considering a rate of LKR 12 per liter or 50 cents per gram of sugar in the product. It underwent four revisions and the recent revision to the policy came into force by October 2020 which fixed the rate to be LKR 12 per litre or 30 cents per gram of sugar for beverages with more than 4 g per 100 ml [24].

Mauritius introduced a sugar tax in the year 2013. The taxing policy deals with a charge of ZAR2.21 cents for every gram of sugar exceeding 4 g per 100 mL. South Africa's National Treasury has mentioned that the resulting taxes are to be 10% as per the calculation of ZAR 11.45 per liter and sugar content to be 10.6g per 100m [25]. Both Dominica and Barbados introduced a tax on sugar-sweetened beverages in 2015. Barbados implemented a 10% tax on sugary beverages in order to reduce the prevalence of obesity [26].

The UK government introduced sugar-sweetened beverage taxes in the year 2016. It mainly focused on reducing sugar consumption by implementing a levy on the soft drinks industry [27]. There was a two-tier taxing system in the year 2018 which mainly dealt with reformulating the content of sugary drinks by the manufacturers rather than directly transferring the whole burden over the consumers. For soft drinks with more than 8 grams of sugar content per 100 milliliters, the tax rate was fixed at £0.24 per liter, while those containing between 5 and 8 grams of sugar per 100 milliliters were fixed at a tax amount of £0.18 per liter. But the drinks with less than 5 grams of sugar per 100 milliliters were exempted from the levy. A few beverages like 100% fruit juices, powdered drink mixes, milk, and milk-based beverages were exempted from taxation despite their

sugar content. Due to reformulation efforts, the United Kingdom Soft Drinks Industry Levy (SDIL) greatly showed a reduction in the sugar content of soft drinks which majorly influenced the amount of sugar purchased [28]. Rogers NT et al. investigated whether the Soft Drinks Industry Levy (SDIL), announced in March 2016 and implemented in April 2018, was linked to changes in the incidence rates of hospital admissions for tooth extractions due to caries in children, 22 months after the SDIL's implementation. There was a 12.1% reduction in hospital admissions for tooth extractions due to caries in children aged 0-18 years. Specifically, reductions of 28.6% were seen in children aged 0-4 years and 5.5% in those aged 5-9 years, with no change in older children. These reductions were consistent across most areas, regardless of deprivation. The UK SDIL was linked to a decrease in the incidence rates of childhood hospital admissions for tooth extractions due to caries [29].

Sugar beverage taxes in India

India, the largest consumer of sugar globally, was also the top producer in 2021, with 27.2 million tons. The average global sugar consumption is 22 kg per person per year, but an average Indian consumes 25 kg per year, including regular sugar, sugar from SSBs, and traditional sources like jaggery [30]. India's per capita sugar consumption has significantly increased, rising from 22 grams per day in 2000 to 55.3 grams per day in 2010 [31]. In India, sugar-sweetened beverage (SSB) taxes are implemented as part of the Goods and Services Tax (GST) system. In India taxes on sugar beverages were part of the GST framework, which came into action in July 2017. This GST system followed different tax rates for various goods and services which were fixed by the Ministry of Finance, Government of India. The rate of 8% was fixed for sugar-sweetened beverages and any beverages with added sugars [32]. Deciding and fixing taxes on sugary drinks was a public health strategy to combat the increased consumption of sugary drinks. Combining these taxing systems with public education on healthy diets and better access to nutritious foods can help encourage the knowledge and understanding of the public in relation to oral health. A study by Gupta A et al. assessed the impact of a 20% price increase on sugar and sugar-sweetened beverages (SSBs) in India. This was a decision analytical model that dealt with predicting the price hike that could prevent an average of 1.32 carious teeth per person over a lifetime and significantly help in prevention of 28 million tooth-loss incidents and cuts down ₹3116.32 billion which are spent in dental treatment. There can be a reduction of up to 0.86% in caries incidence with a similar increase in the sugar-sweetened beverage taxes. This study has suggested that increasing the cost of sugar-sweetened beverage taxes can help reduce caries incidence and further reduce the treatment costs spent on dental disease [33]. There are states like Kerala where they introduced a ‘Fat Tax’ to deal with the increased incidence of obesity and lifestyle-related health issues. This taxing policy aimed to implement a tax on foods that are high in sugar and fat, such as fast foods and processed snacks, which are often linked to unhealthy weight gain and an increased risk of non-communicable diseases (NCDs). In 2016, the Kerala government imposed a Fat Tax to create awareness among the public with policy-driven intervention in order to reduce the prevalence of obesity. The tax was on items such as burgers, pizzas,

doughnuts, and junk food sold in branded restaurants where the taxing policy levied at a fixed rate of 14.5%. The notion behind this strategic approach was decreasing the consumption of nutrient-less and high-caloric foods which greatly offer unnecessary public health burden [30].

Discussion

The World Health Organization in the year 2018 identifies SSBs as major drivers of NCDs due to their high sugar content and lack of nutritional benefits. Sugar-sweetened beverages contribute empty calories thereby providing no energy and offering no health benefits. This characteristic has made them a focal point for both researchers and policymakers [4]. Food labeling, marketing restrictions, and SSB taxes are commonly commended public policies to reduce sugar consumption [34]. The global rise in sugar consumption poses a threat to oral health and requires policy solutions. Ample evidence exists for SSB taxes to counteract this trend, but the oral health community should realize that other factors are at play than evidence-based arguments for oral health alone [35]. Sugar-sweetened beverages (SSBs), including carbonated soft drinks, energy drinks, sports drinks, electrolyte drinks, cordials, and fruit or vegetable drinks with added sugars, are among the largest sources of free sugars in the diets of children and adults [36]. The sugar-sweetened beverage taxes aimed to reduce the increased consumption of sugary drinks by setting high costs over these beverages thereby leading to less intake of sugary drinks. Both economic and public health challenges are addressed by imposing sugar-sweetened beverage taxes. These taxing policies aimed to decrease the incidence of dental caries and other health-related events.

Arora A. et al. conducted a longitudinal study where they assessed the influence of sugar-sweetened beverages in Australian children from birth to age 3 years and found both early life and socioeconomic factors greatly influence the outcomes. They used data from the Healthy Smiles Healthy Kids Birth cohort which had the details of 934 mother-infant pairs. Two different SSB intake trajectories were observed which comprised high and low trajectories. The consumption of sugar-sweetened beverages increased for both groups between 4 months and 2 years and then it got stabilized. Households with three more children, low-education mothers, and those who were residing in socioeconomically disadvantaged areas were found to report high consumption go sugar sugar-sweetened beverages with a rate of 25%. Early intervention to limit sugar-sweetened beverage consumption can help in improving children's nutrition. Socioeconomic factors show a strong correlation in shaping the intake pattern of sugar-sweetened beverages [37]. The sugar-sweetened beverage taxes alter the food intake pattern at individual, family, and community levels. By making people less inclined towards sugar-sweetened beverages it helps to create a healthier environment. This strategy of policy approach not only addresses the immediate health concerns associated with SSBs but also promotes public health and prevents the long-term economic burdens associated with oral health disease.

Economic benefits

1. By imposing sugar-sweetened beverage taxes it aids in generating sufficient economy for the government. Such revenue generated through sugar-sweetened beverage

taxes can help in planning, initiating, and executing oral health programs. It will help in offering subsidies for healthier food and drink.

2. It can help in lowering the incidence of dental caries and other health-related issues. It will also reduce the burden on the healthcare system which sufficently leads to save the cost of dental treatment.
3. It helps to improve the overall oral health-related quality of life. Good oral health offers less discomfort improves productivity and lessens frequent absenteeism in schools and the workplace.

Challenges

1. The sugar-sweetened beverage taxes affect lower-income individuals due to its disproportionate distribution. However, the health benefits and amount generated through SSB taxes surpass all these challenges.
2. The industrial sector often discouraged the concept of SSB taxes because it led to unemployment at a wider scale. Certain pieces of evidence have also mentioned that these SSB taxes created economic downfall.
3. By implementing SSB taxes enhances the knowledge of individuals towards healthy diets, and encourages increased access to affordable healthy foods and drinks.

Recommendation

1. Allocation of SSB tax helps to generate revenue to fund oral health education and provide greater access to underserved communities.
2. By imposing a tax on sugar content naturally reduces the sugar level in beverages by the manufacturers themselves.
3. Through educational programmes creates awareness about the direct link between sugar consumption and oral disease.
4. The direct engagement of healthcare providers to will in the promotion of reduced sugar consumption through constant reinforcement of messages during each dental visit.
5. The stakeholders, public health experts, policymakers, and community groups, can design and implement the tax.

Conclusion

The Global SSB tax has facilitated the guidance on effective SSB taxation principles. Sugar beverage taxes offer a promising public health plan to overcome the increasing burden of oral health. By reducing the consumption of high-sugar drinks these SSB taxes can provide valuable insight on the causes of dental caries, gum disease, and other health-related issues. The success of the SSB tax was directly associated with societal norms around sugar consumption. The strong law and policy system at the global level offer a substantial impact on the reduction of chronic diseases that associated with high sugar consumption. The revenue generated through SSB tax should used wisely over preventive care and health education. In order to create a healthier future the SSB taxing policy should be followed with great responsibility.

Author's Contribution

GR: Conceptualisation, Literature Search, Writing – Original Draft. **VKB:** Supervision, Validation, Writing – reviewing and editing. **SF:**

Conceptualisation, Literature Search, Writing- reviewing and editing. **SV:** Conceptualisation, Literature Search, Writing – reviewing and editing. **ASTL:** Supervision, Validation, Writing – reviewing and editing. **AS:** Writing – reviewing and editing. **ARR:** Conceptualisation, Literature Search,Writing – Original Draft

Conflicts of interest

The authors declares that they do not have conflict of interest.

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CASE REPORT

A Case Report on a Rare Entity: Nerve Sheet Myxoma

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Abstract

Nerve sheath myxoma is a rare benign tumor of peripheral nerve sheath origin arises from the Schwann cell. In 1969 Harkin and Reed first reported a case of Nerve sheath myxoma. The benign tumor clinically present as a nodular soft tissue swelling. Microscopic features are well circumscribed, varying sized nodules comprising of stellate cells in a myxoid background. The cells show diffuse positivity for S100. Nerve sheath myxoma to be differentiated from Neurothekoma, Myxoid Neurofibroma, Myxoid Schwannoma and Perineuroma.

Keywords: Peripheral nerve sheath tumour, Nerve sheet myxoma, Stellate cells, Neurothekoma, S100

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Introduction

Nerve sheath myxoma (NSM) is a benign tumour of peripheral nerve sheath origin, frequently found in extremities [1]. Incidence of nerve sheath myxoma was found more common in young adults [2]. The tumour commonly present as a non-tender, nodular lesion. The microscopic features are multiple myxoid nodule of varying size composed of stellate cells in a myxoid background. Previously nerve sheath myxoma and neurothekeoma were considered to be a related lesion but recent studied showed evidence of its discrete nature [3]. NSM show diffuse positivity for S100 and negative for EMA [4]. Differential diagnosis to be considered for NSM are neurothekeoma, myxoid neurofibroma, perineurioma and myxoid schwannoma [5].

Case History

A 2 years old girl presented with complaints of swelling in the right foot in 4th toe since one month. On Clinical Examination, the swelling was measuring 1.5 cm across, on the subcutaneous plane which was focally attached to the overlying skin. The swelling was soft, non-tender, non-pulsatile and slowly increased in size. X-ray examination showed well circumscribed, hypodense mass noted on the 4th toe of the right foot. Excisional biopsy was done. Grossly we received a well circumscribed, globular mass measuring 1.5x1x0.5cm. Cut surface homogenous, grey white with focal area showing mucoid material. Microscopic examination showed multiple well defined myxoid nodule of varying size which are separated by fibrous septae. The nodules were composed of stellate cells embedded in a myxoid stroma. Immunohistochemical marker S100 and EMA was performed, which showed diffuse positivity on S100 and Negative for EMA (Figures 1-3).

Figure 1. Show a soft tissue swelling measuring 1.5x1 cm on the right foot in 4th toe.

Figure 2. Show a well circumscribed hypodense mass.

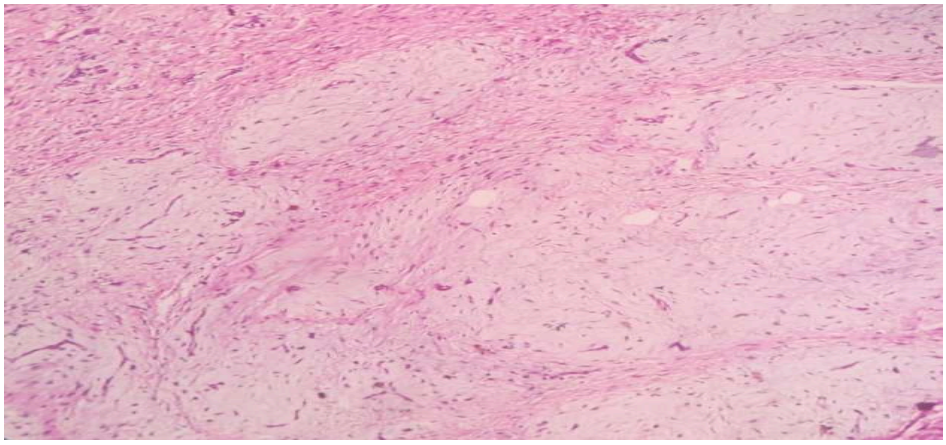

Figure 3. Shows multiple well defined myxoid nodule of varying size composed of stellate cells embedded in a myxoid stroma, which was separated by fibrous septae.

Discussion

Nerve sheath myxoma is benign tumor of peripheral nerve sheath origin arising from the Schwann cells. Nerve sheath myxoma was first reported by Harkin and Reed in the year 1969 [6]. Clinical presentation of nerve sheath myxoma is plainless nodular swelling with indolent growth pattern. Incidence of Nerve sheath myxoma was found in young adult with male to female ratio of 1:1 to 1:2 [7]. Commonest location of NSM is in the extremities with few cases have been reported in head and neck. Previously NSM and Neurothekeoma were considered to be a related tumor of peripheral nerve sheath origin but in recent

days, several studies showed evidence of difference between these two entities by means of clinical, histopathological features, immunohistochemical and genetic features [8]. Gross presentation of NSM is a well circumscribed, firm, multinodualr lesion. Cut surface grey white with myxoid areas. Microscopic features of NSM show a well-defined nodules of varying size which are separated by fibrous septae. The nodules are composed of stellate cells in myxoid background [9]. Immunohistochemical markers show positive for NSM are S100, GFAP and Negative for EMA. Differential diagnosis to be considered for NSM are Neurothekoma. Myxoid neurifibroma, Myxoid schwannoma and Perineuroma [10]. Nerve sheath myxoma need to be differentiate from neurothekoma by histomorphology and immunohistochemistry. Neurothekoma originate from fibroblast and resembles fibrous histiocytomas. It exhibit three different subtypes-cellular, myxoid and mixed. Neurothekomas are negative for S100 and positive for EM. Myxoid Neurofibroma is a unencapsulated tumor predominantly composed of spindle cells arranged in fascicles and whorls admixed with mast cells in a fibrillary and myxoid background. Neurites in Myxoid Neurofibroma show positivity for neurofilament protein. Myxoid schwannoma composed of spindle cells arranged in alternating hyper (Verocay A) and hypocellular (Verocay B) areas in a myxoid stroma. Perineuroma is a well demarcated, unencapsulated lesion composed of spindle cell (fibroblast-like) with variable degree of cellularity in a sclerotic stroma with foci of myxoid degenaeration.

Conclusion

In the present study we report a case of nerve sheath myxoma. Nerve sheath myxoma needs to be differentiated from other spindle cell tumors by clinical presentation, gross examination, histomorphology and immunohistochemtry. However Immunohistorychemistry play a vital role in diagnosing the spindle cell lesions and also guide us in arriving at the right diagnosis.

Statements and Declarations

Conflicts of interest

The authors declares that they do not have conflict of interest.

Funding

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CASE REPORT

A Rare Case of Elbow Tophus: Clinical, Radiological, and Histopathological Findings

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Abstract

Introduction: Gouty tophi represents an uncommon outcome of prolonged gout. The urate crystal deposition in soft tissues characterizes it. They can present as tender, soft tissue masses, mimicking benign growths. Elbow tophi are uncommon but can cause significant morbidity. **Case Report:** A 65-year-old man with a history of chronic gout came in with noticeable swelling on the outer side of his right elbow. The swelling was firm in consistency, non-fluctuant, and mildly tender. Radiological and Histopathological investigations confirmed the diagnosis of tophaceous gout. A successful surgical excision was performed with uneventful post-operative results. **Conclusion:** This case study emphasizes the significance of suspecting tophaceous gout in individuals presenting with significant, unexplained swellings, especially in patients with a known history of gout. Prompt recognition and proper treatment are essential to avert further complications.

Keywords: Elbow tophi, chronic gout, gouty arthritis, urate arthropathy

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Introduction

Gout is defined as a metabolic condition marked by increased levels of serum urate, which causes monosodium urate (MSU) crystals to accumulate in both joint and non-joint tissues. This can lead to recurrent episodes of joint inflammation [1]. In males, serum urate concentrations typically reach their highest levels at puberty, with a range of 5-6 mg/dL. In contrast, normal urate levels in females are considerably lower, averaging between 1-1.5 mg/dL Chronic gout may present with the deposition of MSU in soft tissues and skeletons such as tophi. Tophi may exist in bones and soft tissue places (e.g., skin, synovium, tendons, and ligaments [2–4]. The consistency of tophi may vary from inspissated, chalk-like deposits to semiliquid. Its firm diagnosis requires joint aspiration and demonstration of MSU under polarized light as negatively birefringent needle-shaped crystals [5]. Imaging helps to diagnose this disease. Plain X-rays can show erosive alterations due to chronic and repeated inflammatory episodes. Magnetic resonance imaging (MRI) proves useful for detecting tophi [6].

Case Presentation

A 65-year-old male from the Congo, who has a history of chronic gouty arthritis, came to us with a significant swelling on the extensor side of his right elbow. He was a non-vegetarian and was overall a healthy person with no medical comorbidities like chronic kidney disease, diabetes, and hypertension. He was not taking any uricosuric drugs for his gout and was only consuming non-steroidal anti-inflammatory drugs (e.g., Diclofenac and Ibuprofen) during the acute attacks of pain. The swelling, measuring 10x6 cm, had been gradually increasing over the last five years. The onset was gradual, and it slowly got bigger, sometimes causing pain. There were no signs of fever or any systemic symptoms associated with it. Upon physical examination, the swelling was found to be firm to hard, not fluctuating, unable to be reduced, and did not allow light to pass through. It was slightly painful, not attached to the skin, with no signs of venous prominence, and was fixed to the structures beneath it (Figure 1).

Figure 1. Clinical photograph of the right elbow, showing significant swelling (tophi) over the olecranon

The patient had a full, pain-free range of motion of the elbow joint without any neurovascular deficit, and the systemic examination was unremarkable, indicating the absence of other health issues. Haematological investigations revealed a raised serum uric acid level, i.e. 9.7 mg/dl, and the erythrocyte sedimentation rate (ESR) was normal. Radiographs of the left elbow showed a significant soft tissue shadow (Figure 2).

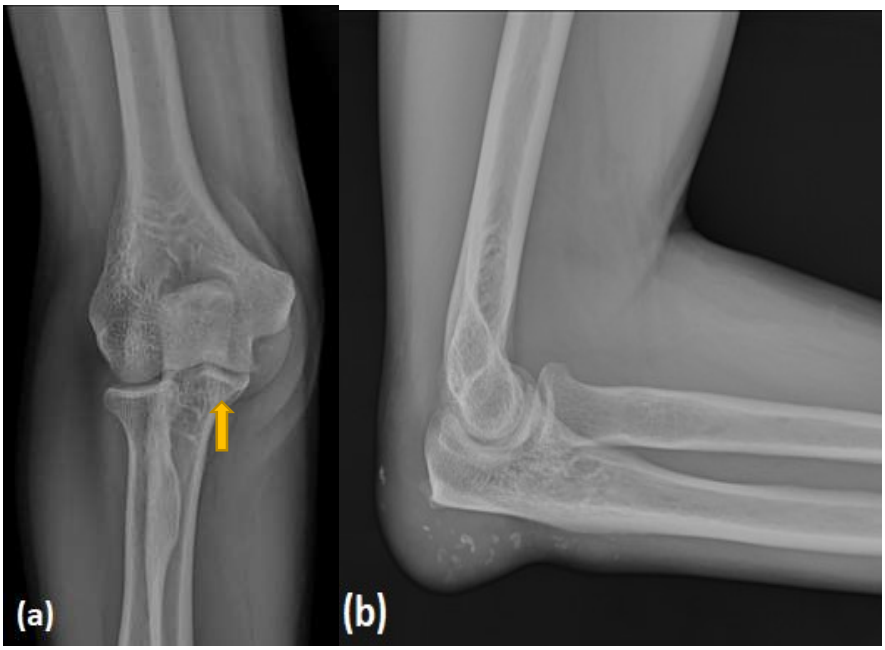

Figure 2. Radiographs *(a)* Antero Posteior (AP), *(b)* lateral show the preserved bone density of the bones. There are multiple calcified tophi seen in the olecranon bursa without adjacent erosion/destruction of the olecranon process (Fig. 2b).

MRI revealed a distended bursa with multiloculated mixed-intensity fluid, with inflammatory changes and thickening in the surrounding soft tissues. Multiple focal areas of blooming representing calcific foci were seen. The inflammatory changes were seen extending up to the insertional point of the triceps tendon, resulting in changes in tendinosis. No evidence of overt tear was noted. All these findings suggested olecranon bursitis secondary to gout (Figure 3). Joint aspiration was not considered in this case, to demonstrate crystals, as the swelling was extra-articular.

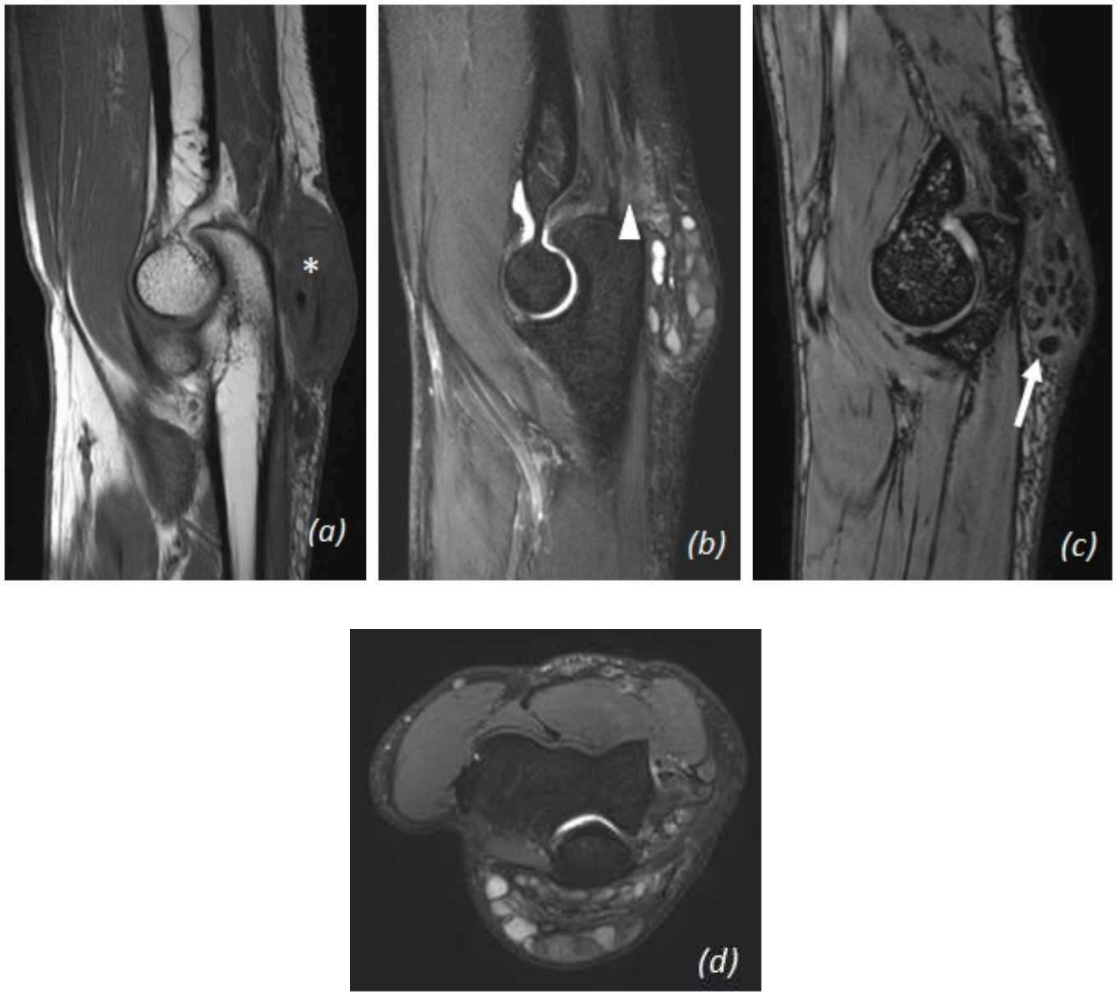

Figure 3. Magnetic Resonance Images of elbow-Sagittal *(a)* T1, *(b)* T2 FAT SAT, *(c)* SWI images show multiple focal areas of blooming (arrow in *(c)*) within the distended bursa representing calcific foci. The inflammatory changes extend up to the insertional point of the triceps tendon, resulting in changes in tendinosis (arrowhead in *(b)*). No evidence of overt tear was noted. Axial (*d)* T2 FAT SAT images showing distended olecranon bursae with multiloculated collections and calcific foci.

The surgical excision of the large right elbow tophi was performed under general anaesthesia. An en-bloc excision of the swelling was performed using a standard posterior approach. The procedure involved making an incision over the swelling, carefully dissecting the surrounding tissues to isolate the tophi, and then removing the tophi in one piece. The excised mass, which was found to be a white, chalky material, weighed 250 grams (Figure 4).

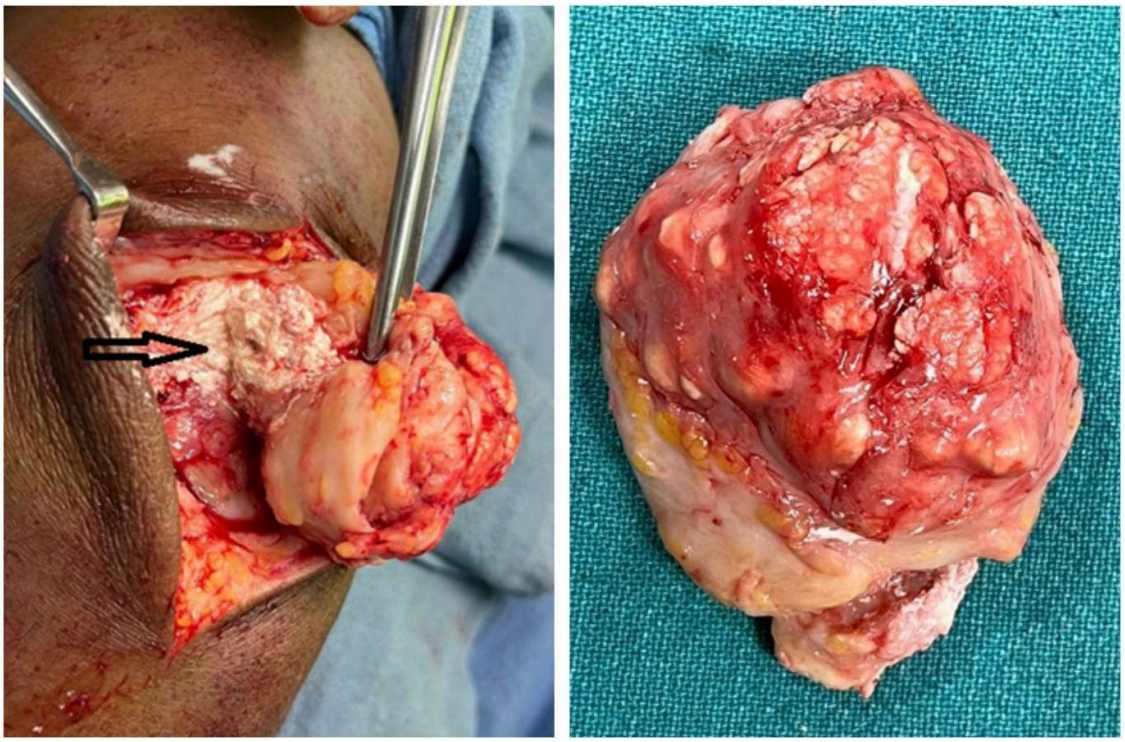

Figure 4: An excised mass of tophi (6.5×4.5×4 cms, 250 gms), arrow showing whitish, chalky material.

Histological examination of this single globular soft tissue piece measuring 6.5×4.5×4 cm (Figure 4) revealed an external surface of the smooth mass, which was shiny and focally fibrofatty. On cut open, yellow-white and whitish material was observed. A few cysts are noted, varying from 0.1 cm to 1.5 cm, and a few calcified areas are seen. Microscopically (Figure 5), there was fibro-collageneous tissue showing oedema and nodular aggregates with granuloma-like appearance consisting of acellular, amorphous, pale eosinophilic material with needle-like spaces surrounded by a palisading arrangement of histiocytes and occasional multinucleated giant cells, few lymphocytes and plasma cells. There was evidence of vascular dilation with haemorrhage, and areas of calcification were seen. Our diagnostic studies, both histopathological and radiological, confirmed the diagnosis of tophaceous gout.

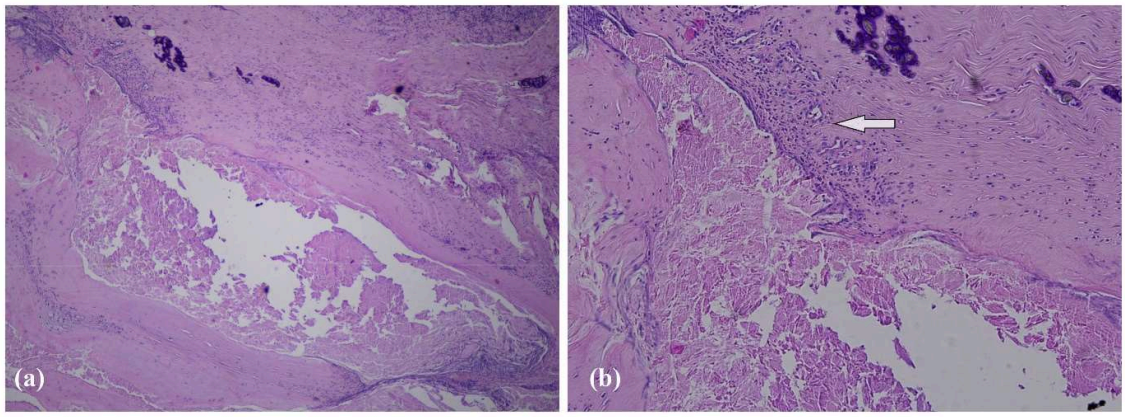

Figure 5 (a- 40x, and b-100x magnification): Histological images showing the palisading arrangement of histiocytes (arrow) and occasional multinucleated giant cells, fibro-collageneous tissue and areas of calcification, suggestive of a tophus.

Postoperatively, the wound healed uneventfully, and the patient had a full range of motion without any neurovascular deficit, further validating our diagnosis. The patient was discharged with post-operative care instructions and scheduled for follow-up visits to monitor his recovery and ensure the absence of any complications.

Discussion

Gout is a systemic condition related to the metabolism of purines. It leads to elevated levels of uric acid and is characterized by typical, recurrent episodes of arthritis [7], with a prevalence rate of 1 to 4% [8]. A study from the USA (from 1989 to 2009) revealed a twofold increase in the incidence of gout and comorbidities over the 20 years [9]. Similarly, a UK study showed an escalation of the prevalence of gout, from 1.52% to 2.49%, between 1997 and 2012 [10]. With increasing prevalence, complications also had an escalating trend with varying presentation in chronic cases. In our case, a 65-year-old male patient presented with a large elbow mass. It is more than three times more common in males as compared to females.

Chronic tophaceous gout occurs in about 10 years in patients who do not receive treatment, with 12–35% of these individuals developing tophi [11,12]. The cutaneous manifestation of gout is tophi, which is an intradermal lesion or subcutaneous nodule. Typically observed in avascular tissues, it is especially prevalent over the ears, at the olecranon and prepatellar bursae, or in extremity locations, frequently in conjunction with tendons [5].

Extensor surfaces of distal extremities are most commonly involved. It is less commonly present around the elbow, especially when it first appears in an asymptomatic patient. The exact prevalence of elbow tophus is not known [13]. The fundamental pathology involves urate crystals invading and causing the destruction of skin, ligaments, tendons, cartilage, and bone due to an inflammatory response at the affected site.

Differential diagnoses for elbow tophi may include other soft tissue masses, such as lipomas or ganglion cysts, which

can present with similar symptoms but have different characteristics on imaging and histopathological examination.

Uricosuric medications and xanthine oxidase inhibitors can effectively stabilize and decrease tophi size. However, approximately 5%-10% of cases remain unresponsive to such conservative treatments [12]. Especially in large tophus, these therapies took time to act and sometimes years to resolve the tophus when able to maintain serum urate levels low. So, it is not suitable for patients requiring urgent relief like having an infection, neurovascular complications, functional disability, etc. [14]. Our case also did not respond to the medical management.

The surgery is recommended in chronic tophaceous gout in the presence of unsightly painful tophi, infection, impending skin necrosis, ulceration and discharging sinus, impairment of tendon function, painful joint destruction, nerve compression, and cosmesis [15-17]. Surgical treatment of gouty tophi has good results and is the first-line treatment for large tophi and faster relief. Surgical management includes excision, curettage and debridement of tophi. However, it is associated with increased rates of skin necrosis and delayed wound healing due to compromised blood supply [18]. Another surgical technique is the arthroscopic shaver technique, which is helpful for the cosmetic debulking of large tophi in advanced tophaceous gout. It is associated with decreased wound complications and can be done in compromised local skin and infection [19]. Generally, tophi are painless but can be painful when associated with local complications like infection, ulceration and acute gout flare. We did surgical treatment in our case as the mass was tender and progressively increasing despite conservative measures with urate-lowering therapies.

In the surgical technique we use, we take a thick cutaneous flap as much as possible and excise the mass till the triceps is involved, including some part of the tendon. Closure of the wound was done without leaving any dead space with absorbable sutures in deeper tissues; redundant skin was excised and closed using non-absorbable sutures under the drain. A compression bandage was given for one day. We found no wound-related complications or reoccurrence at three months of follow-up However, the patient was counselled about the need for longer and regular followup to observe and manage any recurrence or complication.

Conclusion

We presented a rare case of a large elbow tophi in a patient with chronic gout. Surgical excision was a successful treatment option in this case. Prompt recognition and proper treatment are essential to avoid complications related to tophaceous gout. This case underlines the significance of including tophi in the differential diagnosis when encountering large, unaccounted-for swellings, especially among individuals with a gout history.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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CASE REPORT

Caecovesical Fistula Resulting From Foreign Body Injury to Perianal Region: A Rare Occurrence

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Abstract

Colovesical fistula is a recognized condition, most commonly due to diverticular disease. However, traumatic injuries, especially those involving foreign bodies, present a unique etiological factor requiring prompt intervention. We document the first case of a caecovesical fistula caused by foreign body due to perianal injury highlighting the importance of being vigilant in trauma patients with chronic unexplained lower urinary tract symptoms.

Keywords: Colo vesical fistula (CVF), Caecovesical fistula, Foreign body injury, Traumatic injury

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Case Discussion

A 25-year-old man presented to us with complaints of recurrent diarrhoea, burning micturition, intermittent abdominal pain and occasional fever for a period of 10 months for which he was on medical treatment in local hospital. He gives history of fall onto a piece of wood in the jungle a year prior, injuring the perianal region for which he was managed in a local clinic and the wound was sutured. Abdomen was soft with mild tenderness in lower abdomen. Rectal examination showed no abnormality. Hemoglobin 10.3 mg/dl Total leukocyte count: 14270/mm^3

Creatinine: 1.9 mg/dl

Urine had numerous red blood cells, pus cells and bacteria.

Cystoscopy found Large foreign body ~5 cm in the urinary bladder, both ureteric orifices were visualised. Colonoscopy showed oedematous mucosa in caecum with encased faecal matter.

NCCT abdomen identified a large hyperdense structure in the urinary bladder with thickening and right ureteric dilatation.

MRI abdomen detected an intravesical rounded structure 7.8 cm X 3 cm with irregularly thickened urinary bladder with moderate bilateral hydronephrosis and acute pyelonephritis (Fig. 1). Given his clinical history and radiological findings of a foreign body an exploratory laparotomy was proposed and executed. Intraoperatively, a caecovesical fistula caused by a foreign object was discovered (Fig. 2a and b). The fistula was dismantled and foreign body removed following which bladder wall and the caecum were primarily repaired. An omental patch was sutured to the bladder wall. Additionally, a suprapubic catheter (SPC) was placed, and a diversion ileostomy was performed. Postoperative period was uneventful.

Figure 1. MRI showing elongated foreign body (Orange arrow)

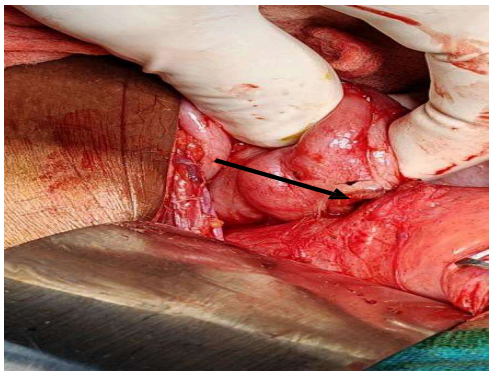

Figure 2a. Caecovesical fistula (Black arrow)

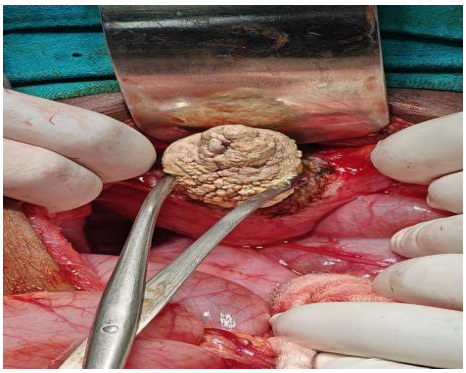

Figure 2b. Foreign body being extracted out

Discussion

Colovesical fistulas representing abnormal connections between the colon and bladder, are complex clinical conditions with various causes. The most common cause is colonic diverticulitis, leading to fistula formation due to inflammation and perforation [1]. Other causes include neoplasms, inflammatory bowel diseases like Crohn's, radiation therapy, and trauma [1]. These varied etiologies require a broad differential diagnosis in patients with unexplained lower urinary tract symptoms, pneumaturia, fecaluria, and recurrent infections [2]. Diagnosing colovesical fistulas can be difficult, especially when the underlying cause is atypical or symptoms are mild. Although diverticulitis remains the most frequent cause, there have been few reports in literature about colovesical fistulas due to foreign bodies perforating the bowel and creating a fistulous connection with the bladder. Foreign bodies ranging from chicken bones [3], modeling-knife blades [4], and biliary stents [5] have been reported. In patients presenting with chronic unexplained lower urinary tract symptoms, intravesical foreign body is to be kept into consideration as it can remain undiagnosed for prolonged periods [6]. Although there is an isolated case of congenital caecovesical fistula [7] this is the first reported case of caecovesical caused by foreign body due to traumatic injury to perianal region. During the work up of suspected colovesical fistula, cystoscopy and colonoscopy play a role during the initial workup [8]. However more detailed radiological studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are required as they play an increasing role in diagnosing and planning of management of colovesical fistula. Cross-sectional imaging with CT scan gives detailed information often revealing air or contrast in the bladder, while MRI offers superior soft tissue contrast, aiding in visualizing the fistula and surrounding inflammation [2,9]. Colovesical fistula typically mandates surgical intervention and it usually involves removal of the of any foreign body, resection and repair of the affected bowel segment and oversewing of bladder defect [10]. In the current era, laparoscopic approach to managing colovesical fistulas in high-volume colorectal surgery centres is both effective and safe as it offers an edge over open surgery in terms of reduced surgical site infections and fewer medical complications. However, in patient with ongoing sepsis and persistent inflammation involving the bowel, bladder, and pelvis, faecal diversion alone or along with resection may be required to decrease symptoms and control sepsis [11].

Conclusion

Colovesical fistula is an uncommon clinical condition and it requires a collective

team approach for management. This case highlights the need for considering rare entities such as foreign bodies as a cause of colovesical fistula especially in patients with a history of trauma increasing the etiological spectrum of this condition. Early diagnosis and timely surgical intervention are critical to prevent further complications and to restore the patient's quality of life.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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Consent to participate and publish

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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LETTER TO THE EDITOR

Concerns and Observations on Mehndi Oil Poisoning: A Call for Awareness

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Mehndi oil is a mixture of essential oils derived from plants such as Eucalyptus (Eucalyptus globulus), Tea tree (Melaleuca alternifolia), Ravensara (Ravensara aromatica), and Cajeput (Melaleuca cajuputi). Eucalyptus oil contains eucalyptol, α-pinene, myrcene, cineole, fenchone, α-terpinolene, camphor, and β-terpinyl acetate [1,2]. Tea tree oil contains various terpene compounds, with terpinen-4-ol being the most prominent [3,4]. Ravensara oil is rich in estragole (methyl chavicol) and eucalyptol [5]. Cajeput oil's main active components are cineole and terpineol [6]. Commercially available mehndi oil typically contains terpenes like eucalyptol (40-80%), limonene (5-15%), and alpha-terpineol (3-7%), which enhance henna's dye release.

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Eucalyptus oil is commonly used to relieve respiratory issues such as cough and cold, soothe sore muscles, and act as a natural insect repellent and disinfectant. Tea tree oil, Ravensara oil, and Cajeput oil are often used in skincare for treating acne and fungal infections, as well as in hair care to fight dandruff. Additionally, all these essential oils are used as antiseptics in wound care.

Mehndi oil enhances the colour and longevity of mehndi, a natural dye used for cosmetic purposes in the Indian sub-continent. The oil is rich in terpenes, which interact with the hennotannic acid (lawsone) in mehndi leaves (Lawsonia inermis) to create a deeper and more vibrant stain. Lawsone dissolves well in mehndi oil compared to water due to its chemical properties *(like dissolves like).* It is pertinent to mention that lawsone has several applications ranging from

cosmetics to biomedicine and its therapeutic potential is being actively investigated by the research community [7].

Commercially available Mehndi oil preparations (Figure 1) are usually smooth, light, non-greasy in consistency; transparent to pale yellow and sometimes orange in colour depending on the concentration of its constituents and have a characteristic camphoraceous aroma. However, the labels on mehndi oil products often do not explicitly list all the ingredients in the mixture, which may include various artificial compounds beyond the essential oils/standard ingredients typically used, intended to serve the same purpose.

A 33-year-old male employee at a tattoo shop in a metropolitan city accidentally ingested about 30-70 ml of a transparent liquid, mistaking it for water. The liquid, later identified as mehndi oil, had been transferred to a water bottle for regular use at his work place. Mehndi oil (which is sometimes referred to as tattoo oil), used to enhance stain brightness, is a mixture of various essential oils as mentioned above. After ingestion, the individual experienced multiple episodes of vomiting and was taken to a nearby hospital for initial treatment. He was then admitted to a tertiary care hospital in an altered state of consciousness with a poor Glasgow Coma Scale (GCS = 6) score and was irritable. Within a few hours, his condition deteriorated before any blood/radiological investigations could be performed. Despite resuscitative efforts, he succumbed due to aspiration pneumonitis (clinician's notes) approximately nine hours after the incident and three hours after being admitted to the tertiary care hospital. An autopsy was subsequently conducted in this case as it was mandated by the law.

The postmortem examination revealed several significant findings. There was marked laryngeal oedema, and the trachea contained pinkish white froth. The oesophagus showed the presence of a yellow, tenacious fluid. The liver, lungs, and kidneys were congested, and the stomach contained approximately 200 ml of dark yellowish fluid with a camphor-like odour, along with congested mucosa and haemorrhagic patches (Figure 2).

Microscopic examination revealed pulmonary oedema, interstitial oedema, inflammation with focal lymphoid aggregates, and congested blood vessels in the lungs. The liver showed sinusoidal and central vein dilatation with congestion. Both kidneys exhibited congestion with areas of acute tubular necrosis. The stomach had lymphoid aggregates in the lamina propria and submucosa (Figure 3).

Chemical analysis of the preserved viscera (stomach and its contents, proximal part of small intestine and its contents, liver with gall bladder, kidneys and blood) identified the presence of Alpha pinene, a terpenoid compound. The cause of death in this case was attributed to Alpha pinene toxicity (mehndi oil/eucalyptus oil poisoning).

Although mehndi oil is considered safe for topical application, it exerts systemic toxicity when accidentally ingested. The toxic effects of eucalyptus oil, which is one of its major constituents, typically manifest quickly within a few minutes and include symptoms such as a burning sensation in the mouth and throat, abdominal pain, and spontaneous vomiting. Early central nervous system (CNS) effects may include dizziness, lack of coordination, and confusion, which can progress to loss of consciousness within 10 to 15 minutes. While convulsions are rare in adults, they

are more frequently observed in children. In adults, fatal outcomes are generally associated with the ingestion of around 30 ml, although cases of death have been reported with as little as 4 to 5 ml [1]. True eucalyptus oil, derived directly from the eucalyptus tree, does not contain camphor. However, eucalyptus oil produced from the cineole fraction of camphor laurel (often referred to as "fake eucalyptus oil") may contain camphor. Similar to eucalyptus oil, camphor also has epileptogenic properties [2].

Accidental ingestion of eucalyptus oil in children has been reported to lead to seizures, while in adults, although seizures are less common, toxicity can manifest as severe metabolic acidosis, neutrophilic leucocytosis, and mild elevation of liver enzymes. Overall, epileptogenicity followed by CNS depression has been highlighted in previous case reports. The use of gastric lavage or activated charcoal is not advocated due to equivocal outcomes. There is no specific antidote for eucalyptus oil poisoning, and treatment is supportive [1,2]. Interestingly, several studies also indicate the antimicrobial and anti-inflammatory properties of eucalyptus oil. However, the concentration and dosing of the substance require strict caution [8].

Tea tree oil (TTO) another major constituent in mehndi oil, is used in cosmetic and pharmaceutical products. Its major constituents include terpinen-4-ol and 8-cineole, among others. Terpinen-4-ol is a bactericidal substance known to destroy cell walls and affect protein or DNA synthesis [9].

The outcomes of TTO consumption vary from mild skin irritation to systemic toxicity. However, no deaths have been reported due to TTO poisoning so far. Clinical symptoms include central nervous system depression characterized by an unsteady "drunk" state, and ataxia in children, unconsciousness, unresponsiveness, often accompanied by hallucinations in the elderly. Other less serious manifestations include urticaria and hypersensitivity responses. Irritant reactions are often concentration-dependent and do not rely on previous exposure to the irritant. TTO is a known contact allergen and can cause dermatitis.

Tea tree oil (TTO) has been proposed as a treatment for otitis externa and otitis media due to its antimicrobial properties. However, studies in guinea pigs have shown that TTO can cause ototoxicity, as well as hepatotoxicity and nephrotoxicity. Despite these findings in animal studies, no such toxic effects have been observed in humans under typical usage conditions. Several studies have assessed the toxic effects of TTO and its components on human cell lines in vitro, though data on the ecotoxicity of TTO are limited. The toxicity of TTO against fish, amphibians, insects, worms, and other aquatic and terrestrial species or ecosystems has not been thoroughly assessed [10].

Ravensara oil is as a flammable liquid and poses toxicological risks, including dermal and ocular irritation, skin sensitisation with prolonged exposure, and potential germ cell mutagenicity and carcinogenicity. It also presents an aspiration hazard upon inhalation, leading to potential pulmonary injury, and is environmentally hazardous with ecotoxicity concerns. Cajeput oil, while also causing dermal and ocular irritation, primarily presents risks upon ingestion, where it can lead to systemic toxicity. Chronic exposure may result in respiratory discomfort, though data on its mutagenic,

carcinogenic, and teratogenic potential remains insufficient.

The misconception that 'eucalyptus oil' and 'tea tree oil' being considered as an 'innocuous herbal remedy' should be reconsidered, as both eucalyptus oil and tea tree oil are known to cause systemic toxicity with lethal outcomes and consequences when ingested. The lethal dose (LD50) data of the major ingredients of mehndi oil are mentioned in Table 1 [11-14]. The therapeutic potential of the essential oils mentioned above remains an area of ongoing research. Their bioactive compounds are being studied for potential benefits in areas such as antimicrobial, anti-inflammatory, and analgesic effects.

This may be the first documented case of fatal mehndi oil poisoning, as all previously reported cases involve poisoning from individual components such as eucalyptus oil or tea tree oil. An important toxic manifestation of clinical concern is laryngeal edema, a feature commonly encountered in super-vasmol (hair dye) poisoning in South Asian clinical toxicology practice. Like with hair dye poisoning, an early intervention with tracheostomy may play a significant role in decreasing the mortality along with supportive care.

It is advisable that mehndi oil, eucalyptus oil, and tea tree oil be packaged in a way that prevents copious amounts from being dispensed at once. Fixed-volume, single-use containers should be employed to avoid transferring these substances to other containers where they might be mistaken for water, leading to accidental ingestion, as seen in this case. Additionally, incorporating specific dyes or indicator colors into these substances could help prevent confusion with water. However, this raises concerns about the commercial viability of such products, as incorporating indicator dyes may impact their efficacy, which is another area that requires further research.

There is a need for regulatory reform about the packaging, labeling, and sale of these substances, with clear indications of their toxicity on the containers/ depiction of hazard signs, symbols. Clinicians should also be made aware of such poisoning cases and their signs and symptoms to help prevent fatalities.

Table 1. LD50 values of key essential oils commonly used as ingredients in Mehndi oil/Tattoo oil

S. No	Compound	LD50
1	Eucalyptus oil	3320 mg/Kg BW
2	Tea Tree oil	1.9-2.6 ml/Kg BW
3	Ravensara oil	Eucalyptol: 2480 mg/Kg BW Estragole: 1230 mg/Kg BW
4	Cajeput oil	3870 mg/Kg BW

Figure 1. Representational images of **A** Eucalyptus oil (yellow-tinged to transparent), **B** Tea tree oil (pale yellow to transparent), and **C** Mehndi oil (transparent to brown).

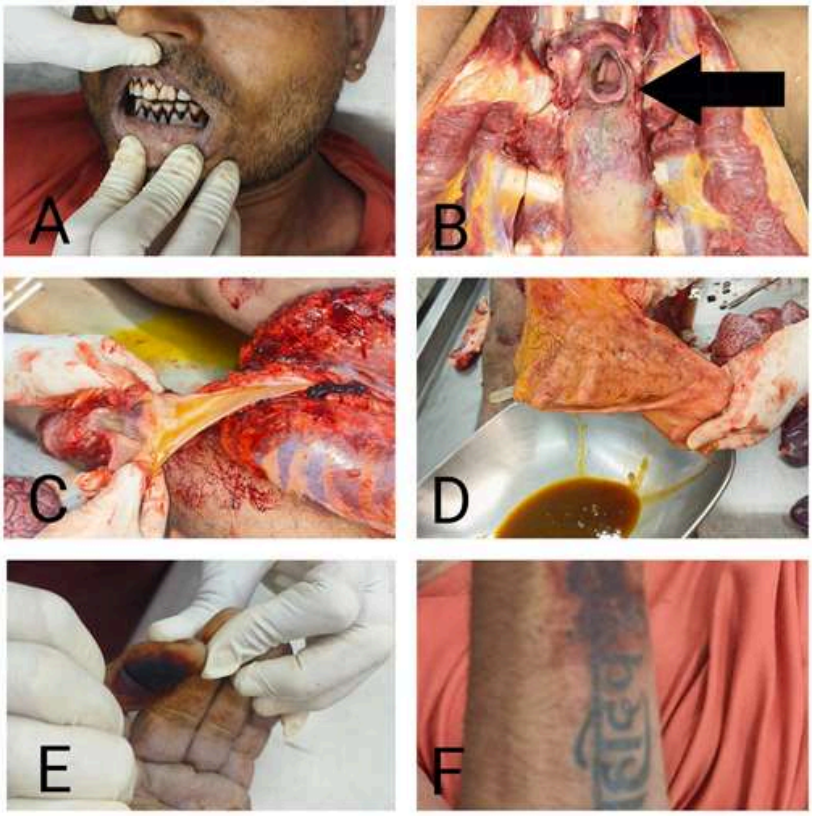

Figure 2. Autopsy findings **A** Reddish brown staining of teeth due to tobacco abuse **B** Laryngeal oedema, **C** Yellowish tenacious fluid in oesophagus **D** Haemorrhagic stomach mucosa **E** Fingers showing mehndi stains (occupational stigmata) **F** forearm showing mehndi stains (occupational stigmata).

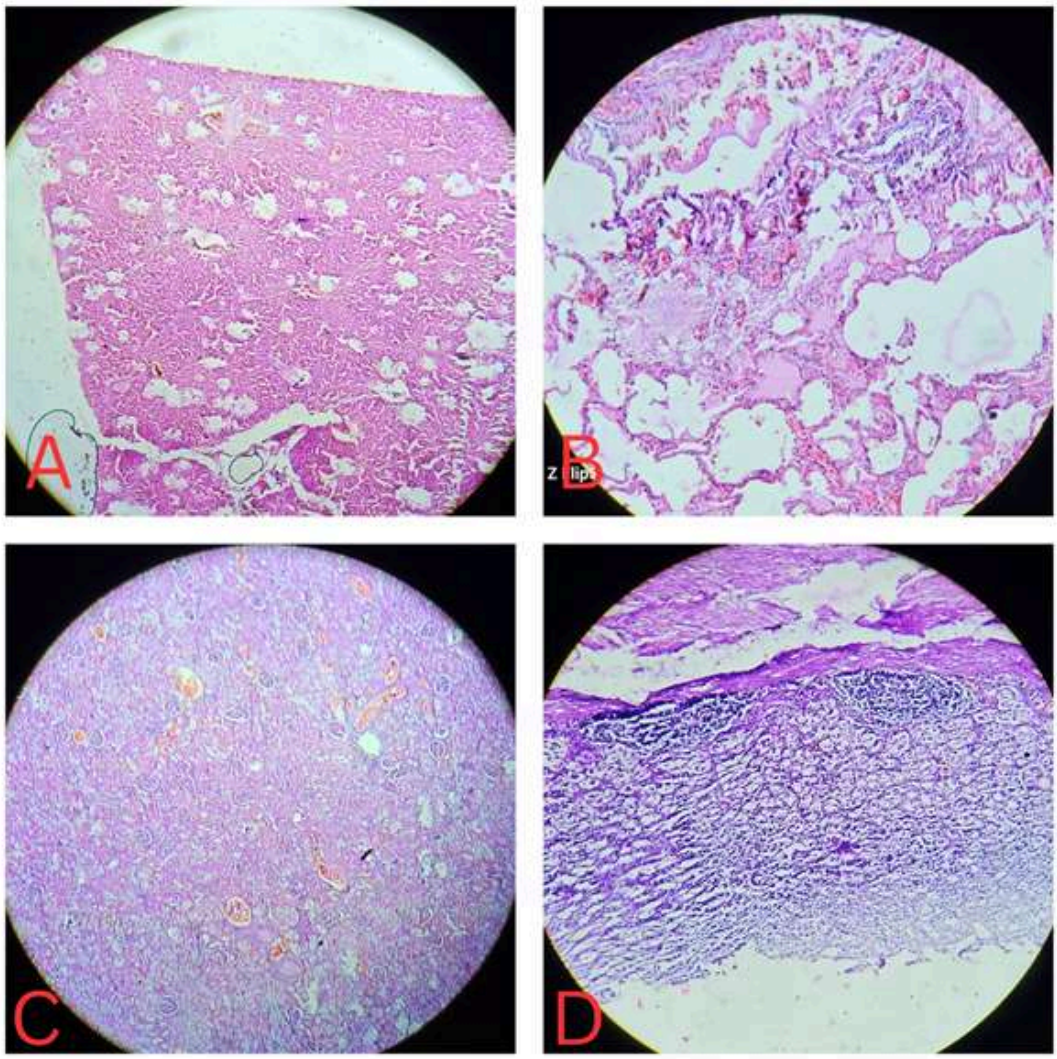

Figure 3. Histopathological Findings **A** Liver showing sinusoidal dilatation and congestion H&E 10X, **B** Lung showing oedema and inflammatory infiltrates H&E 10X, **C** Renal tissue showing congestion and acute tubular necrosis H&E 10X, **D** Stomach showing lymphoid aggregates H&E 10X.

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Limitations

Information regarding the deceased's general health condition prior to the incident was unavailable, and a quantitative analysis of alpha-pinene in the blood (both antemortem and postmortem) could not be performed due to limited resources. Additionally, the sample of Mehndi oil involved in this fatality was not subjected to toxicological analysis.

Conflicts of interest

The authors declares that they do not have conflict of interest.

Funding

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Ethical Considerations

Addressed by the authors.

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