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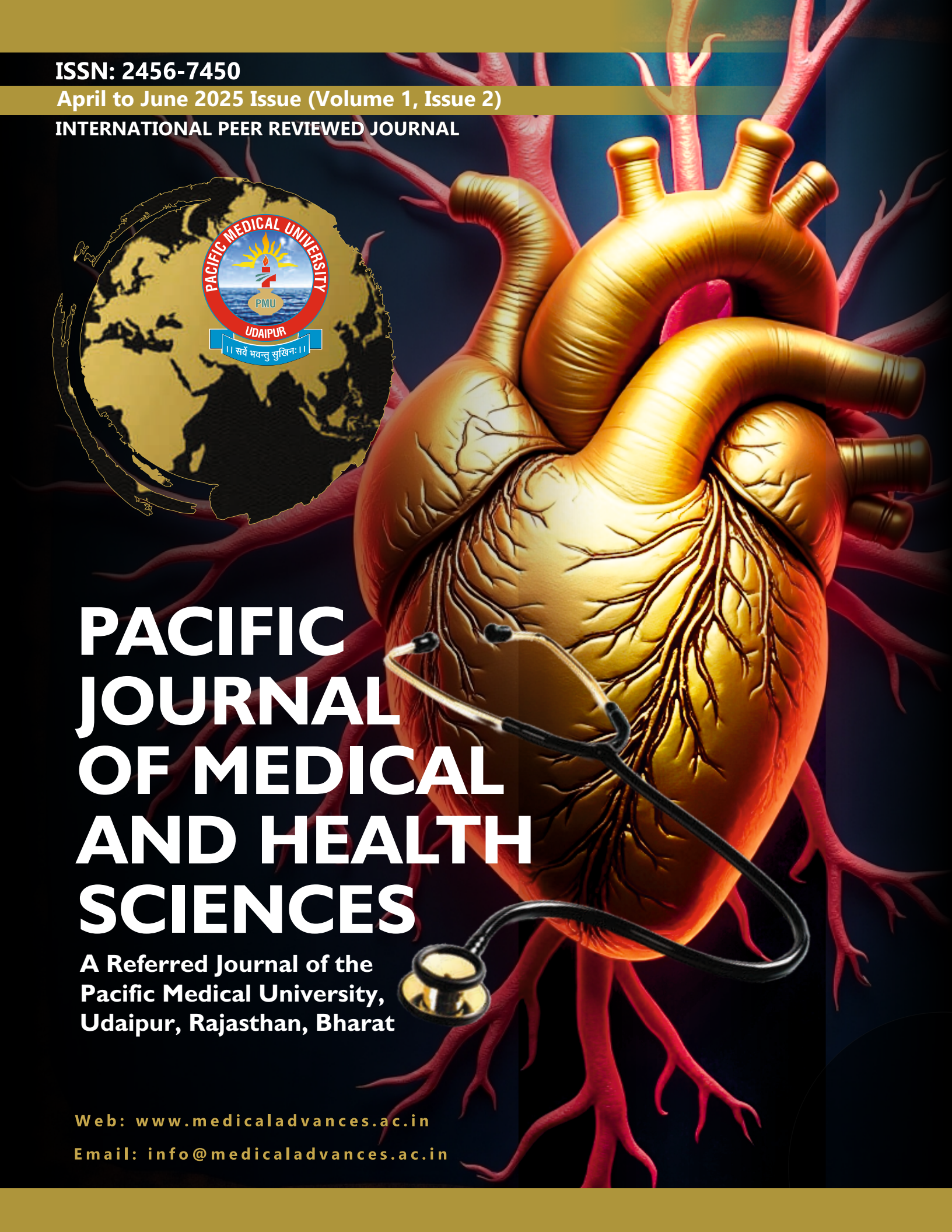

PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

A Referred Journal of the Pacific Medical University, Udaipur, Rajasthan, Bharat

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Pacific Journal of Medical and Health Sciences

PJMHS
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General Information

The Journal

Pacific Journal of Medical and Health Sciences (ISSN: Print - 2456-7450) is a Multidisciplinary, International Peer Reviewed Quarterly Journal of the Pacific Medical University, Udaipur, Rajasthan, Bharat.

The Journal is published quarterly in the months of January, April, July and October.

The subject areas for publication include Multidisciplinary Subjects within Medical Sciences, viz., Anatomy, Anaesthesia, Biochemistry, Biomedical Sciences, Cardiology, Community Medicine, Dermatology and Venereal Diseases, Diabetes, Endocrinology, Epidemiology and Public Health, Forensic Science, Gastroenterology, Geriatric Medicine, Hematology, Immunology, Infectious Diseases, Internal Medicine, Microbiology, Nephrology, Neurology, Neurosurgery, Obstetrics and Gynaecology, Ophthalmology, Oncology, Orthopaedics, Otorhinolaryngology (ENT), Paediatrics, Pathology, Pharmacology, Physiology, Psychiatry, Pulmonary Medicine, Radiology, Toxicology, Dentistry, Nursing, Health Informatics, and Occupational Safety and Health.

Aims and Scope

Pacific Journal of Medical and Health Sciences is a peer reviewed journal with multidisciplinary approach. The goal of the journal is to publish new, challenging and radical ideas, dedicated to promote innovative and high quality research work in the field of medical and health sciences. The journal provides a platform for advances in basic and advanced clinical medical research for all branches of health-sciences. The journal provides cutting edge updates, developments in the medical arena and helps to synchronise and share knowledge.

The key aims of the Journal are to provide interpretations of growing points in medical knowledge by trusted experts in the field, and to assist practitioners in incorporating not just evidence but new conceptual ways of thinking into their practice.

We focus on the clinical aspects of diseases with basic science contributions in areas of clinical interest.

The journal invites articles related to different aspects of Medical and allied Health Sciences including Dental Sciences. The journal publishes original research articles, reviews, case reports and commentaries. The journal is an important and reliable source of current information on developments in the field of medical and health sciences. The emphasis is always on publishing high quality articles with fast review process.

Please note that Call for Papers, Peer-Review Policy, Reviewers' Guidelines, Publication Ethics and Publication Malpractice Statement and Disclaimer have been provided at the end of the issue.

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Editor's Picks

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Research Paper

Effects of Soursop (*Annona muricata*) Leaf Extract on the Prefrontal Cortices of Maternal and Fetal Wistar Rats

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ABSTRACT

Background:

Annona muricata (soursop) leaf extract contains acetogenins, which inhibit mitochondrial complex I, and alkaloids, known neurotoxins. This study investigates the neuroanatomical and biochemical effects of crude aqueous A. muricata leaf extract on the prefrontal cortices of maternal and foetal Wistar rats.

Materials and Methods:

Twenty-four adult female Wistar rats were randomly assigned to three groups (n=8 each). Treated groups received 0.5 ml of crude aqueous soursop leaf extract during the second and third trimesters, while controls received distilled water ad libitum. Rats were sacrificed a day before delivery via cervical dislocation. Prefrontal cortex tissues were processed for histological examination using Hematoxylin & Eosin staining and biochemical analysis of oxidative stress markers: Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), Glucose-6-Phosphate Dehydrogenase (G6PDH), and Lactate Dehydrogenase (LDH). Serum progesterone and oestrogen levels were also measured.

Results:

Treated groups exhibited a significant increase in SOD and GPx activities ($p<0.05$) compared to controls. Conversely, G6PDH, LDH, progesterone, and estrogen levels decreased significantly ($p<0.05$) in treated groups. Histological analysis revealed a reduction in neuronal density in the prefrontal cortex of treated rats.

Conclusion:

Maternal consumption of Annona muricata leaf extract during pregnancy may lead to oxidative stress, hormonal imbalance, and neuroanatomical alterations in developing foetuses. Given these potential neurotoxic effects, pregnant women should exercise caution, and further research is needed to assess its safety for foetal development.

KEYWORDS: *Annona muricata,* Oxidative stress, Neurotoxicity, Pregnancy, Wistar rats.

BACKGROUND

Teratogens are substances or environmental factors that can cause birth defects in a foetus[1]. These agents disrupt normal foetal growth and can lead to physical malformations, neurological disorders, or even pregnancy loss[2]. Dosokyand Setzer demonstrated that the effects of teratogens depend on the timing of exposure, with the first trimester being the most critical period for organ formation[3]. Broussard and colleagues in their study in 2011 further indicated that the severity of the impact also varies based on the dosage and duration of exposure. Preventing teratogenic effects involves avoiding harmful substances during pregnancy and proper prenatal care against exogenous agents[4].

Reactive oxygen species (ROS) such as superoxide anion radical, hydrogen peroxide, singlet oxygen, and hydroxyl are active forms of reactive molecular oxygen[5]. ROS are bye product of normal metabolism of oxygen within the mitochondrial matrix, which acts as their precursor serving as physiological regulator of normal cell multiplication and differentiation[6]. If the balance of ROS increases more than the scavenging potentials of the intracellular antioxidant system, the cell undergoes a state of oxidative stress which impairs significantly the cellular structures and functions. However, excessive levels of ROS, often result in severe damage to DNA and proteins[7].

Complementary medicine includes a diverse range of traditional and alternative healing practices that are used alone or alongside conventional Western medicine[8]. These approaches are deeply rooted in cultural beliefs, indigenous knowledge, and the rich biodiversity of most continents of which Arica is not left out. Natural medicinal plants often exert their effects through several mechanisms including oxidative stress depending on their bioactive components[9].

Soursop (*Annona muricata*) is a medicinally valuable traditional medicinal plant across tropical regions because of the well-known antioxidant and anti-inflammatory effects of its leaves, bark, root, and other components[10]. Biochemical studies on leaves of *Annona muricata* have detected anxiolytic, anti-inflammatory, and anticonvulsant properties as well as neuroprotective properties[11]. The plant is a rich source of alkaloids, and flavonoids together with acetogenins[12]. However, the safety limit and potential neurocytotoxic effects of crude aqueous extracts of soursop leaves on the developing brain, particularly the pre-frontal cortex(PFC), remain largely unexplored.

The Pre-frontal cortex (PFC) is known to play a vital role in decisions making, social and emotional regulation[13]. Developmental changes in this region before birth strongly impact neuronal functions which conversely impairs cognitive functions and behavioral manifestations[14]. The periods of organogenesis are usually a pivotal point in teratogenic interference of the developmental process[15]. The gestational development of the PFC becomes vulnerable because of multiple factors that include environmental toxins as well as pharmaceuticals and herbal remedies[16].

Brain development of foetuses faces potential risks when pregnant women are exposed to bioactive compounds from plants[17]. Studies have shown both protective and toxic neurological outcomes in connection with CBD usage which depends on how much CBD is given and how long people use it[18].

This research aims to examine the gestational brain structural alterations of maternal administration of crude aqueous soursop leaf extract on the prefrontal cortices of both mother and pups of Wistar rats. Focusing on neurodevelopmental safety and effects through evaluation of both histological and neuronal densities together with investigations into potential neuroprotective or neurotoxic impacts.

MATERIALS AND METHODS

Animal Procurement and Breeding

Procurement:

A total of 24 female and 10 male healthy adult Wistar rats, weights (150-200g) were procured from the Department of Veterinary Medicine, University of Ilorin. The rats were transported in plastic transparent cages to the animal facility of the Department of Human Anatomy, Faculty of Basic Medical Sciences College Health Sciences, University of Ilorin where they were transferred into their home cages.

Breeding and Acclimatization:

The rats were acclimatized for two weeks in the animal facility of the Human Anatomy Department, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin.

They were kept under a 12-hour light-dark cycle at room temperature. The male and female rats were housed separately in wooden wire-gauzed cages measuring 12" x 12" x 16". The cage floors were designed with wire mesh to facilitate waste removal. The cages were cleaned daily, and the rats were fed with pelletized feeds (Topfeeds Nigeria Limited, Sango, Ilorin) and provided distilled water *ad libitum*.

Experimental Plant

Fresh *Annona muricata* leaves were collected from the Department of Plant Biology, University of Ilorin. The leaves were air-dried, ground into a fine powder, and sieved. A crude aqueous extract was prepared by dissolving 10g of the powdered leaves in 100ml of distilled water, which was subsequently evaporated to dryness. A final extract concentration of 10g dissolved in 100ml of normal saline was prepared for oral administration.

OTHER MATERIALS

Wire-gauzed cages, rat pellets, feeding trough, dissecting sets, calibrated syringe, oro-gastric tube, measuring cylinder, feeds, staining trough, oven, microtome, sensitive weighing scale, slide cover slips, slides, specimen bottles, hand gloves, dissecting board, cotton wool, xylene, 10% formalin, beakers, glass rods, hot plate, plastic embedding mould, Bunsen burner, paraffin wax, absolute alcohol, distilled water, haematoxylin stain, eosin stain, hydrochloric acid, egg albumin, Distrene Plasticizer Xylene (DPX), forceps, scalpels, surgical blades, paper tape, and permanent markers.

Determination of Mating

Mating was determined using the vaginal smear test to monitor the estrous cycle, which includes proestrus, estrus, metestrus, and diestrus phases. A micropipette containing 0.5ml of normal saline was introduced into the vagina of the female rats between 7:00-9:00 am to collect vaginal secretions. The collected fluids were placed on glass slides and examined under a light microscope (x10 magnification). In rats, ovulation occur in oestrous phase[19]. Ovulation was confirmed during the estrous phase[19], and female rats were paired with males at a 2:1 ratio from 4:00 pm to 8:00 am. The presence of spermatozoa in the vaginal smear confirmed mating and was considered day 0 of pregnancy.

Animal Grouping and Treatment

After pregnancy confirmation, the rats were randomly grouped as follows:

Group	Duration	Treatment (0.5ml)	Administration Duration	No. of Animals	Expected No. of Fetuses
A	2nd Week	0.5ml aqueous extract	Days 9-11	8	8
B	3rd Week	0.5ml aqueous extract	Days 15-17	8	8
C	Control	0.5ml distilled water	Entire gestation	8	8

Tissue Processing for Microscopic Analysis

Fixation and Dehydration:

Fixation and dehydration were carried out using the method of Drury and Wallington (1980). The extracted tissues were fixed in 10% formalin to preserve their structural integrity. Following fixation, the tissues underwent a series of graded dehydration steps to remove water content in preparation for embedding. Initially, the tissues were immersed in 50% alcohol for one hour, followed by subsequent immersion in 70% and 90% alcohol, each for one hour. Finally, the tissues were placed in absolute alcohol in two changes, with each change lasting one hour. This stepwise dehydration process ensured the optimal removal of water from the tissues, facilitating proper infiltration during the embedding phase[20].

Clearing, Embedding, and Sectioning:

This was done using the protocol indicated by Feeback[21]. The clearing was performed using xylene in two changes of 1 hour each. Impregnation with molten paraffin wax (60°C) was done in two changes at 1-hour intervals. Embedded tissues were trimmed, mounted on wooden blocks, and sectioned using a microtome.

Staining Techniques:

The procedure of staining was carried out as described by Bakerand colleagues[22]. Haematoxylin and eosin (H&E) staining techniques were employed to visualize tissue morphology. In this method, haematoxylin stains cell nuclei a blue-black color, while eosin imparts varying shades of red, orange, and pink to the cytoplasm and connective tissues. The haematoxylin solution was prepared using 5 g of haematoxylin crystals, 100 g of calcium alum, 5 ml of 95% alcohol, 100 ml of distilled water, and 2.5 g of mercuric oxide. For eosin preparation, 1 g of eosin Y was dissolved in 640 ml of 95% alcohol and 160 ml of distilled water, with one drop of acetic acid added per 100 ml of the solution[22].

The staining procedure began with dewaxing tissue sections in xylene for 3 to 5 minutes, followed by rehydration through descending grades of alcohol—absolute, 90%, 70%, and 50%. The sections were then rinsed in distilled water and stained in haematoxylin for 12 to 15 minutes. Differentiation was carried out using 1% acid alcohol for approximately 2 seconds, after which the sections were blued under running tap water for 15 minutes. Counterstaining with eosin was performed for 2 to 3 minutes. The sections were then dehydrated through ascending alcohol grades, cleared in xylene, and finally mounted using DPX mountant and covered with a coverslip to preserve the stained tissues for microscopic examination[22].

Photomicrography

Slides were photographed using a Canon Digital Camera (10 megapixels).

Biochemical Assays

Prefrontal cortex samples were preserved in 0.25M sucrose solution, homogenized, and centrifuged at 5000 rpm for 10 minutes using a centrifuge (Model 90-1). The supernatants were stored in the deep freezer (GC-B207WVQ) at – 20°C - 20°C and analyzed for:

- Superoxide Dismutase (SOD)
- Glutathione Peroxidase (GPx)
- Glucose-6-Phosphate Dehydrogenase (G6PDH)
- Lactate Dehydrogenase (LDH)

Superoxide Dismutase (SOD) Assay:

Beauchamp's method was used to measure superoxide dismutase (SOD). To assess SOD activity, both standard and sample solutions (10 µl each) were prepared. To each solution, 200 µl of a radical detector was added. The reaction was initiated by adding 20 µl of xanthine oxidase, and the mixture was then incubated at room temperature for 30 minutes to allow the enzymatic reaction to proceed. Following incubation, the absorbance of each reaction mixture was measured at 450 nm using a spectrophotometer to determine SOD activity[23].

Glutathione Peroxidase (GPx) Assay:

As demonstrated by Weydert, the activity of glutathione peroxidase (GPx) was determined using a spectrophotometric assay. The reaction mixture was prepared containing phosphate buffer, reduced glutathione (GSH), nicotinamide adenine dinucleotide phosphate (NADPH), and glutathione reductase (GR). The enzymatic reaction was initiated by the addition of the sample serving as the enzyme source. Subsequently, hydrogen peroxide or an organic hydroperoxide was added as the substrate to start the reaction. The decrease in absorbance at 340 nm, resulting from the oxidation of NADPH to $NADP^+$, was monitored continuously. GPx activity was then calculated based on the rate of NADPH consumption, using the molar extinction coefficient of NADPH ($6.22 \times 10^3\ M^{-1}\ cm^{-1}$)[24].

Glucose-6-Phosphate Dehydrogenase (G6PDH) Assay:

To check how active the G6PD enzyme is, Minunci demonstration was employed for this study. A buffer was first made using Tris-HCl and magnesium chloride. Then, two important ingredients — $NADP^+$ and glucose-6-phosphate — were added. After that, the sample containing the enzyme was mixed in, and everything was warmed up to 37°C. As the enzyme worked, it caused a change that was measured by watching how the mixture absorbed light at 340 nm. The faster the light absorbance increased, the more active the enzyme was[25].

Lactate Dehydrogenase (LDH) Assay:

Hochella & Weinhouse's description was adopted to measure lactate dehydrogenase (LDH) activity, an assay buffer was first prepared using phosphate buffer. For the forward reaction, NADH and pyruvate were added to the mixture, while for the reverse reaction, NAD^+ and lactate were used instead. The enzyme sample was then added, and the mixture was incubated at 37°C. As the reaction took place, changes in absorbance at 340 nm were monitored over time — either a decrease in NADH or an increase in NAD^+. The activity of LDH was calculated based on how fast the absorbance changed, which reflects the speed of the reaction[26].

STATISTICAL ANALYSIS

The data were analysed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, California, USA) and displayed as mean ± standard error of mean (SEM). Two-way ANOVA were used to test for statistical significance, with a significance level of $p < 0.05$.

RESULTS

BODY WEIGHT CHANGES

The body weights of the pups were taken immediately as they were removed from the mother before they were sacrificed. There was no statistically significant mean difference in the mean body weight of the pups in 2nd week of gestation when compared with the control. Meanwhile, there was a statistically significant reduction in the mean body weight of the pups in the 3rd week of gestation when compared with the control ($p<0.05$). However, the 2nd week and 3rd week of gestation showed no statistical significance in their mean body weight when compared with the control as shown in Figures 8 & 9.

BIOCHEMICAL

At the dosage of 0.5ml administered per oral, Superoxide dismutase (SOD) activities were observed to be elevated to 145.025±4.22 and 130.595±18.66 U/L for mother and foetus respectively, in the treated groups of 3rd week, compare to the control group with values 40.000±2.00 and 65.30±9.33 (mother and pups) as shown in Figure 1. However, there was an increase in the level of GPx in both the mother and pups of the 2nd week and 3rd week of the treated group from 84.500±17.50 and 90.000± 8.00 (U/L) against the control group as shown in Figure 2 while there was observed decrease in the levels of the activity of Lactate dehydrogenase (LDH) in the treated groups slightly when compared with the control group as shown in Figure 3. Meanwhile, there was no statistically significant difference in the activity of G6PDH of the treated groups when compared with the control groups FIG 4. In addition, the results of the hormonal assay involving progesterone and estrogen in the treated groups slightly reduced when compared with the control. However, this decrease was not statistically significant Figure 5.

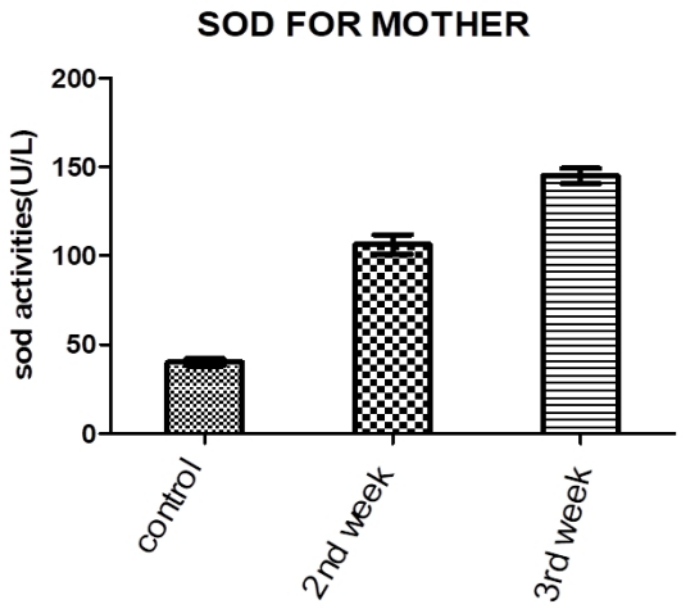

Figure 1: Bar Chart showing the Result of Superoxide dismutase (SOD) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group (Adult Female Rats)

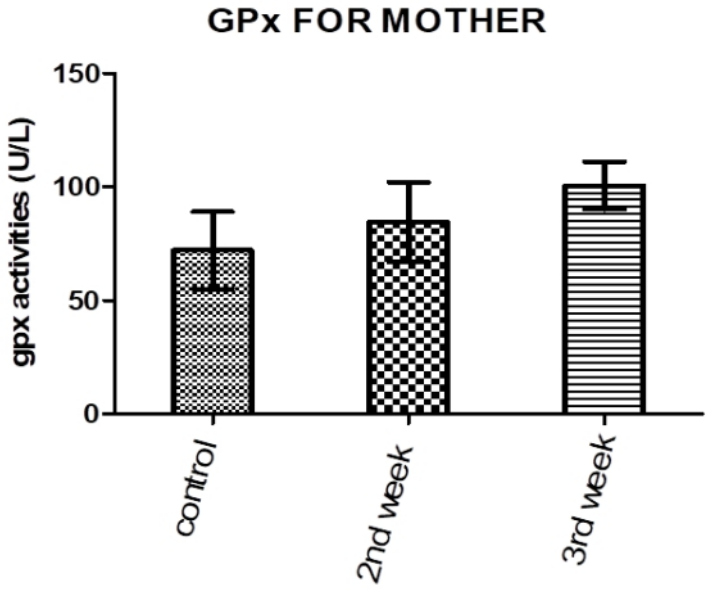

Figure 2: Bar Chart showing the Result of Glutathione peroxidase (GPx) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group (Adult Female Rats)

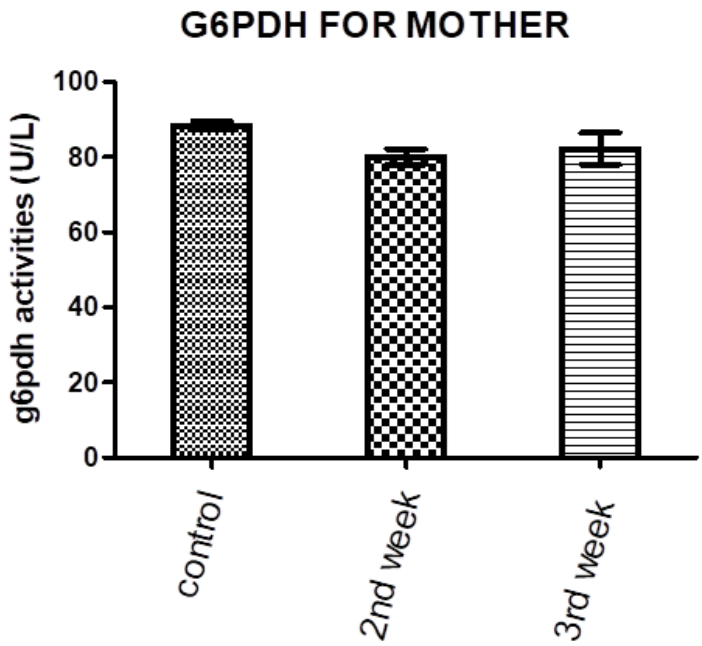

Figure 3: Bar Chart showing the Result of Glucose 6 Phosphate dehydrogenase (G6PDH) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group (Adult Female Rats)

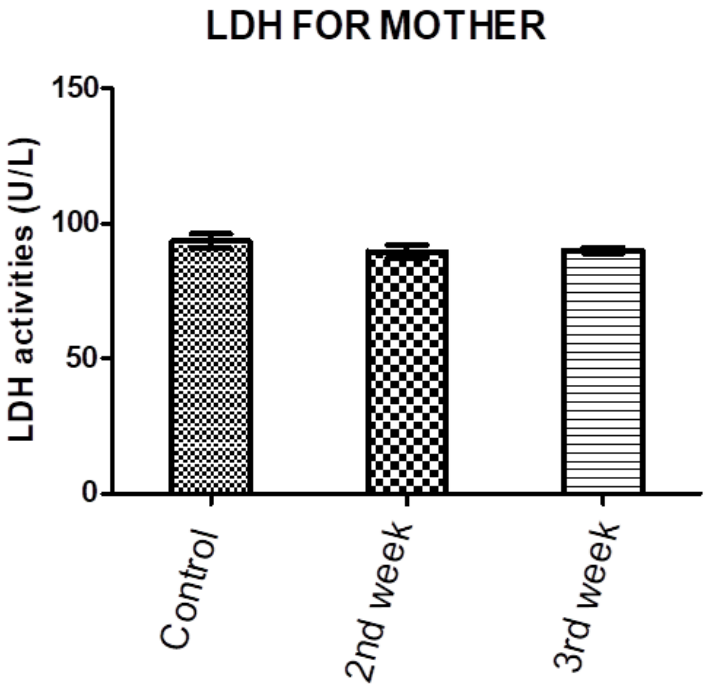

Figure 4: Bar Chart showing the Result of Lactate Dehydrogenase (LDH) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group (Adult Female Rats)

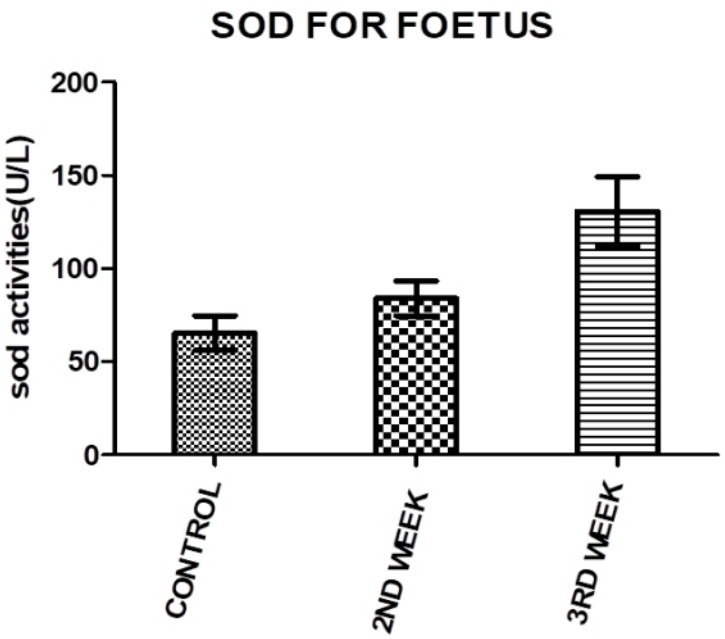

Figure 5: Bar Chart showing the Result of Superoxide dismutase (SOD) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group

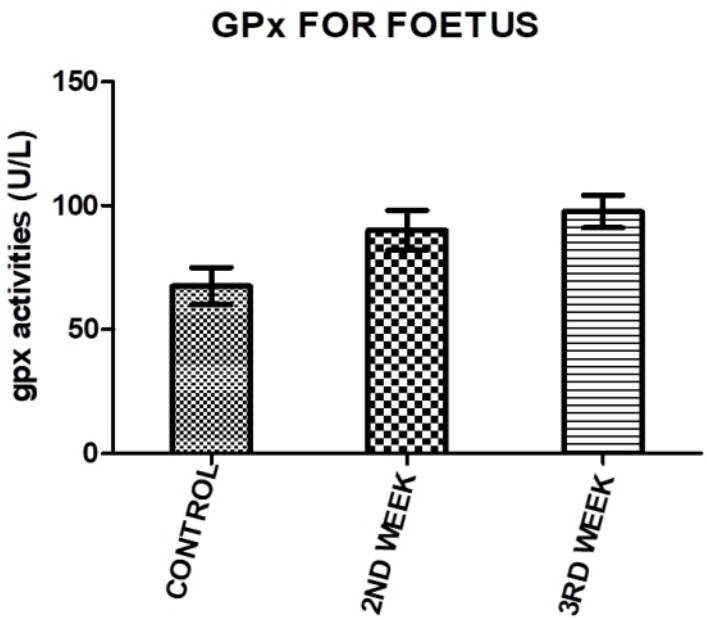

Figure 6: Bar Chart showing the Result of Glutathione peroxidase (GPx) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group

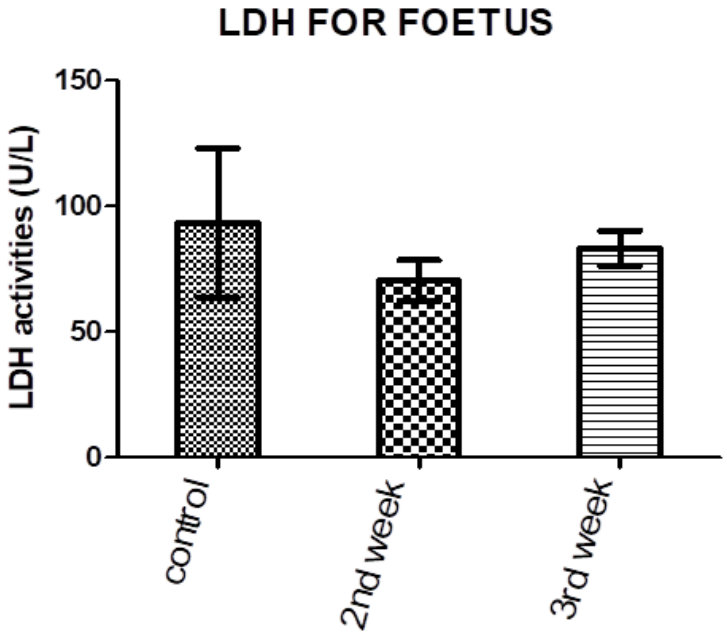

Figure 7: Bar Chart showing the Result of Lactate Dehydrogenase (LDH) Enzyme Analysis exhibiting Control, 2nd Group and 3rd Group (Foetuses)

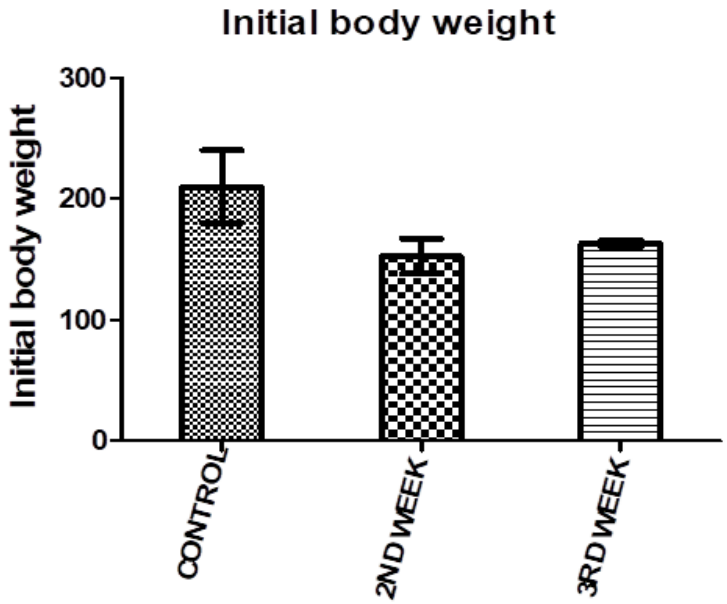

Figure 8: Bar Chart showing the Result of Initial Body Weight Analysis exhibiting Control, 2nd Group and 3rd Group

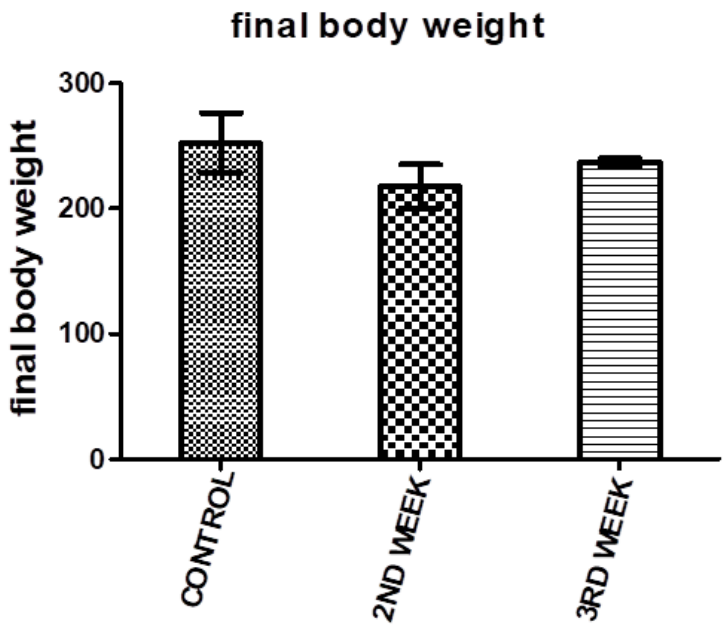

Figure 9: Bar Chart showing the Result of Final Body Weight Analysis exhibiting Control, 2nd Group and 3rd Group

HISTOLOGY

The histological observation revealed normal cytoarchitecture of the pre-frontal cortices of both the mother and foetus of the rats in the control with normal Pyramidal cells as shown in Plates A & D. However, the rats treated with the soursop leave extract at the second trimester revealed several levels of neurodegenerations such as membrane disbandment, cellular aggregation, and vacuolation as evidenced in plates B & E. Meanwhile, the rats that were administered with the extract in their third trimester were observed to have shown mild degeneration of cells when compared with the control as shown in plates C & F.

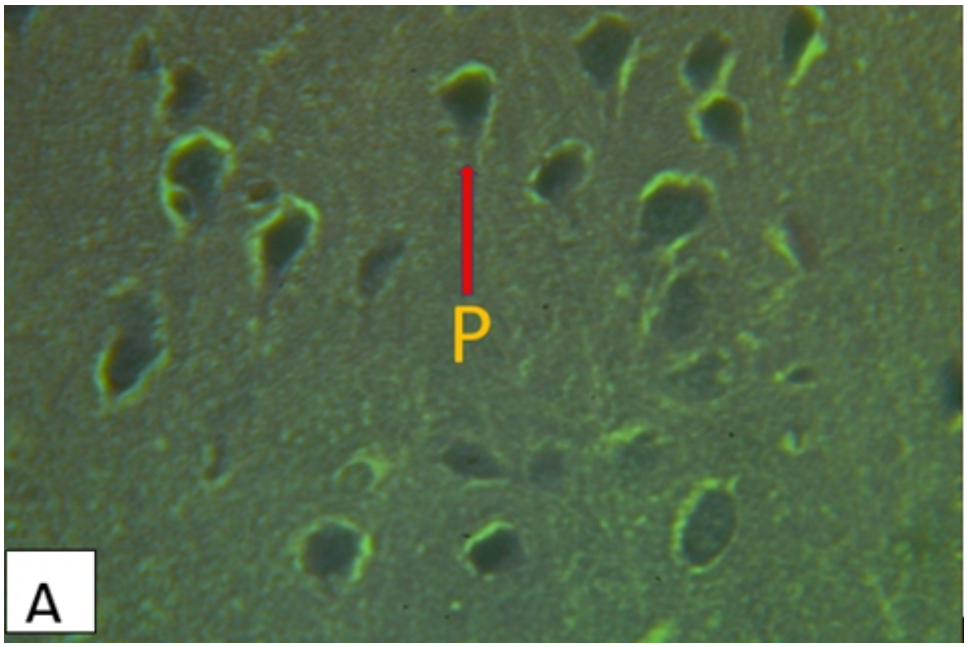

Plate A: Photomicrograph showing Normal Pyramidal Cell (PC) of the Section of the Prefrontal Cortex of Wistar Rat (Mother) in the Control Group using H&E Stain (x400)

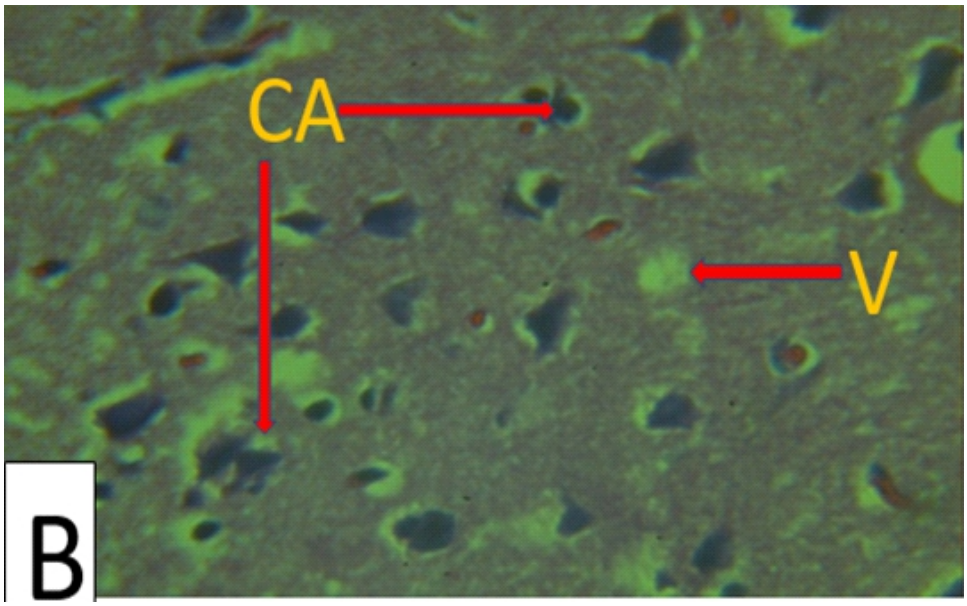

Plate B: Photomicrograph showing Cellular Aggregations (CA), Vacuolations (V) of the Section of the Prefrontal Cortex of Wistar Rat (Mother) in the 2rd Trimester of 2nd Group using H&E Stain (x400)

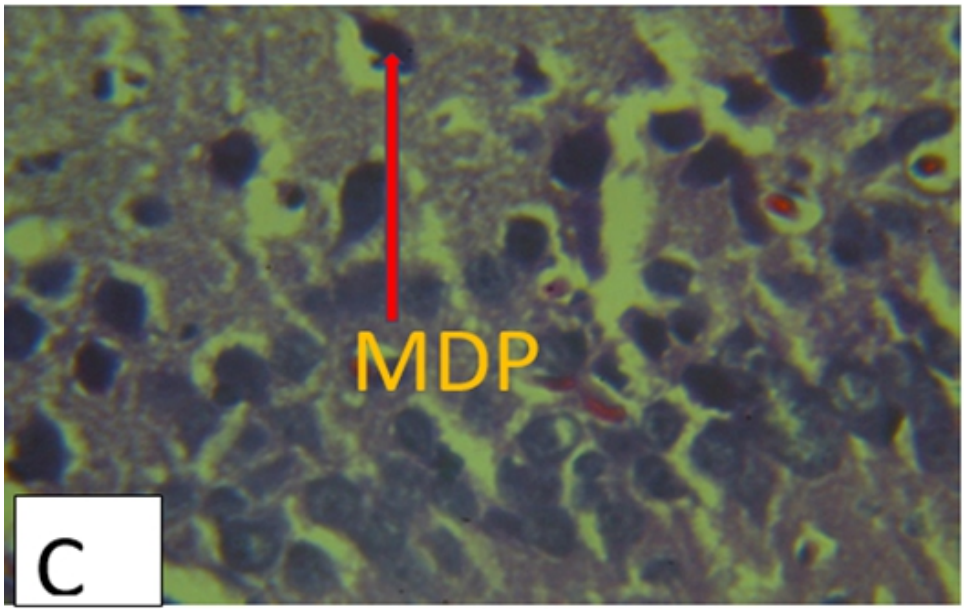

Plate C: Photomicrograph showing Mild Degeneration of Pyramidal Cells (MDP) of the Section of the Prefrontal Cortex of Wistar Rat (Mother) in the 3rd Trimester of the 3rd Group using H&E Stain (x400)

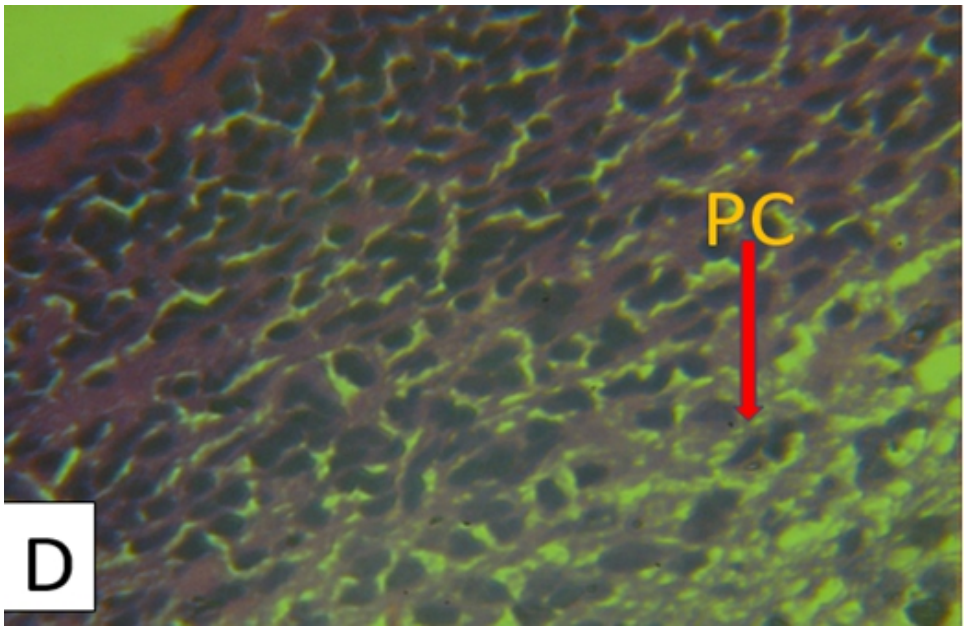

Plate D: Photomicrograph showing Normal Pyramidal Cells (PC) of a section of the Prefrontal Cortex of Young Wistar Rat (Foetus) in the Control Group using H&E Stain (x400)

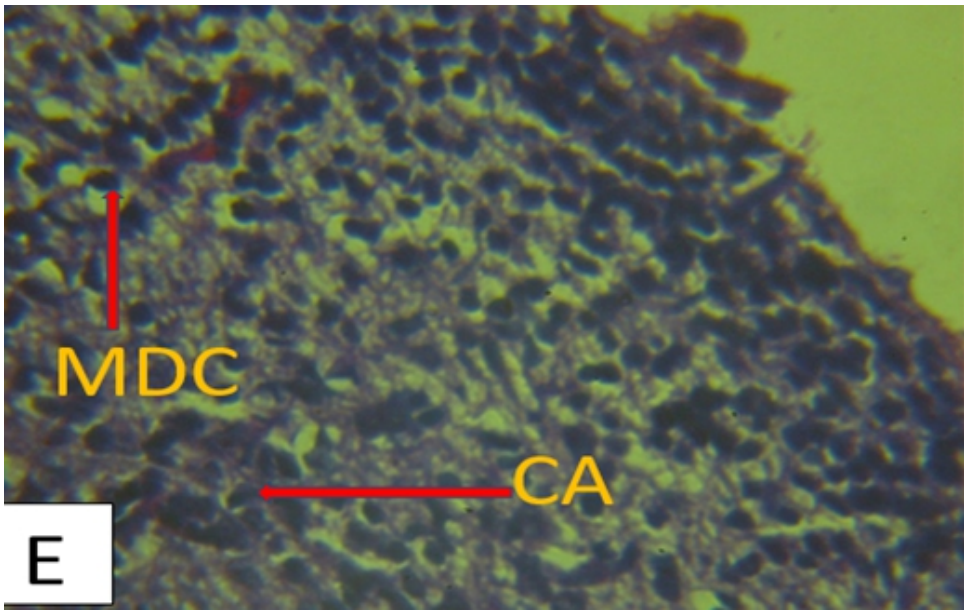

Plate E: Photomicrograph showing Mild Degeneration of Cell (MDC), Cellular Aggregation (CA) of a Section of the Prefrontal Cortex of Young Wistar Rat (Foetus) in the 2nd Trimester of Rats in 2nd Group using H&E stain (x400)

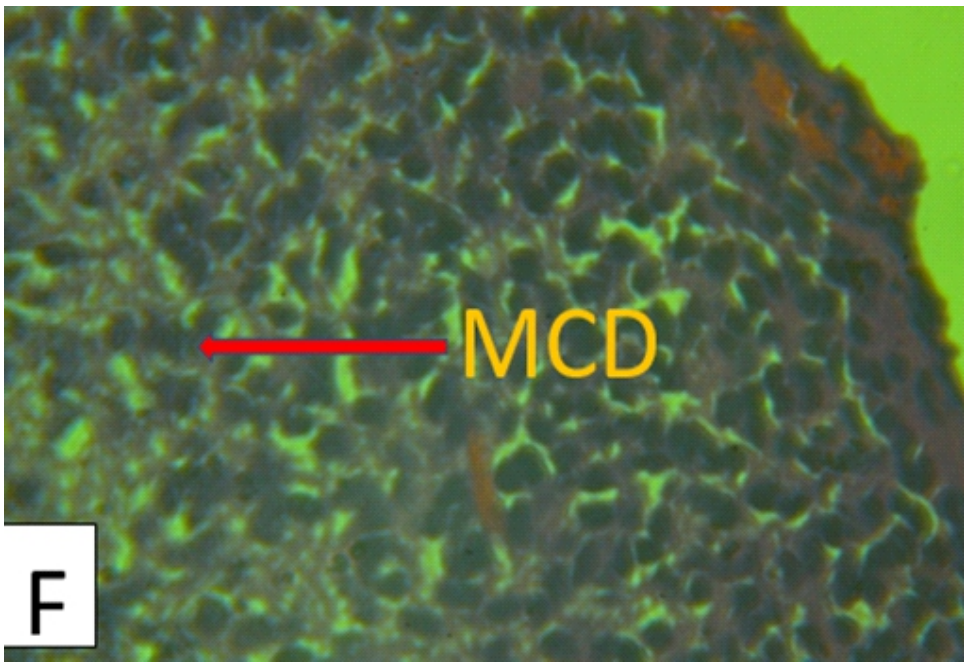

Plate F: Photomicrograph showing Mild Cellular Degeneration (MCD) of a Section of the Prefrontal Cortex of Young Wistar Rat (Foetus) in the 3rd Trimester of Rats in the 3rd Group using H&E Stain (x400)

DISCUSSION

Findings from this study revealed no statistically significant difference in the mean body weight of the pups in the second week of gestation compared to the control group. However, in the third week of gestation, a statistically significant reduction in mean body weight was observed ($p<0.05$). This suggests that while foetal growth appeared unaffected in the early stage, the later stage of gestation may be more vulnerable to the effects of Annona muricata leaf extract.

Superoxide dismutase (SOD) is an enzyme that catalyzes the dismutation of toxic superoxide radicals into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2), which is relatively stable. It plays a crucial role in cellular defense against oxidative stress[27]. Following oral administration of 0.5 mL of the extract, SOD activity significantly increased in pups compared to the control group ($p<0.05$). This suggests an induced oxidative response in the developing brain, potentially leading to redox imbalance. Interestingly, the stability of SOD levels in mothers implies that the plant extract's antioxidant properties may have provided some level of protection in maternal tissues. This aligns with Carole et al. (2022), who also reported a significant increase in SOD activity following Annona muricata extract administration[28].

Glutathione peroxidase (GPx) plays a critical role in detoxifying hydrogen peroxide and mitigating oxidative stress[29]. In this study, GPx levels increased in both mothers and pups during the second and third weeks of gestation in the treated group. Although not statistically significant, this trend suggests an adaptive antioxidant response. This aligns with the findings of Basker et al. (2007), who observed a similar pattern in their in vitro antioxidant study of Annona species leaves[30].

Lactate dehydrogenase (LDH) is a key enzyme involved in cellular energy metabolism and is commonly used as a marker of cell damage[31]. In this study, LDH activity in the treated groups showed a slight decrease compared to the control group. While a decrease in LDH may suggest metabolic adaptation rather than direct neuronal damage, the presence of annonacin, a potent neurotoxin in *Annona muricata* leaf extract, raises concerns about its potential to induce neurodegeneration through the mitochondria-mediated apoptosis pathway[32].

Glucose-6-Phosphate Dehydrogenase (G6PDH) plays a pivotal role in the pentose phosphate pathway, generating NADPH essential for antioxidant defense and biosynthetic reactions[33]. The observed decrease in G6PDH activity in the treated groups compared to the control suggests that the extract may induce metabolic stress, potentially affecting neuronal proliferation and maturation. This finding is consistent with the work of Lannuzel et al. (2002), who identified *Annona muricata* alkaloids and acetogenins as neurotoxic compounds capable of interfering with ATP synthesis and leading to neuronal dysfunction[34].

Teratogens disrupt normal intrauterine development, with the extent of interference depending on gestational age and organ sensitivity[35,36]. The brain, being highly susceptible to exogenous agents, is particularly vulnerable to alterations in neuronal cytoarchitecture[35]. Histological analysis in this study revealed a reduction in neuronal density in the prefrontal cortex of pups exposed to *Annona muricata* leaf extract during the second trimester. Accompanying changes such as vacuolation, membrane disintegration, and cellular aggregation further highlight potential neurotoxic effects. These findings align with Kim et al. (2020), who reported similar neuroanatomical alterations following *Annona muricata* exposure in female Wistar rats[37].

Moreover, Handayani & Nugraha (2015) demonstrated that *Annona muricata* extract induces neuronal degeneration, increases neuroglial proliferation, and contributes to neuroinflammation, particularly in the substantia nigra and cerebral cortex[38]. The photomicrographic analysis in this study corroborates these findings, suggesting that annonacin, a potent neurotoxin present in *Annona muricata* leaves, disrupts mitochondrial function by reducing ATP supply and inhibiting mitochondrial transport, ultimately leading to tau protein dysfunction, neuronal degeneration, and cell damage[39].

These findings suggest that while *Annona muricata* leaf extract exhibits antioxidant activity, its potential to induce oxidative stress, metabolic alterations, and neuroanatomical changes in developing fetuses warrants further investigation. Given the vulnerability of the developing brain to exogenous compounds, caution is advised regarding its use during pregnancy.

CONCLUSION

In conclusion, *Annona muricata* is a potent antioxidant and anti-inflammatory medicinal plant. However, its administration during pregnancy should be carefully considered, particularly concerning the timing and duration of exposure. This study suggests that exposure to *Annona muricata* leaf extract during the second and third trimesters may result in severe teratogenic effects on embryonic nervous tissues and contribute to maternal neurodegeneration.

CONFLICT OF INTEREST: None

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Research Paper

Protective Effects of Lycopene against Propoxur Induced Liver Injury Mediated by Up Regulation of Xanthine oxidase/ Uric Acid Signaling

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ABSTRACT

Background:

Propoxur, a carbamate pesticide, induces liver injury through oxidative stress and inflammation, primarily via the xanthine oxidase/uric acid signaling pathway, leading to increased reactive oxygen species (ROS) production and hepatic damage. Lycopene, a powerful antioxidant in tomatoes, counters oxidative stress and inflammation, but its protective role against propoxur-induced liver toxicity remains underexplored. This study evaluates lycopene's potential in mitigating pesticide-induced liver injury.

Methodology:

Thirty male Wistar rats (average weight: 165 g) were divided into six groups (A–F) of five rats each. Group A served as the control, while Groups B and C were exposed to propoxur (3 ppm) for 30 days, with exposure durations of 5 minutes and 1 hour daily, respectively. Group D received lycopene (10 mg/kg) for 30 days, while Groups E and F were co-treated with propoxur and lycopene.

Results:

Histological analysis revealed liver damage in propoxur-exposed rats, marked by significant weight loss and elevated liver enzymes (ALP, ALT, AST), indicating liver dysfunction. Oxidative stress markers, such as malondialdehyde (MDA) and ROS, were elevated, alongside an increase in interleukin-6 (IL-6), indicating oxidative and inflammatory damage.

Conclusion:

Propoxur exposure resulted in liver injury, oxidative stress, inflammation, and weight loss in Wistar rats, highlighting its toxic effects. Lycopene's antioxidant and anti-inflammatory properties show promise in protecting against pesticide-induced liver toxicity, warranting further investigation into its therapeutic applications.

KEYWORDS: Lycopene, Propoxur, Liver injury, Oxidative stress, Inflammation

INTRODUCTION

Liver problem remains a significant global health issue, with various environmental toxins, pharmaceuticals, and industrial chemicals contributing to its onset. Among these, pesticides, particularly organophosphates and carbamates, are widely used in agriculture and domestic settings to control pests, but they pose substantial risks to human health and the environment. Propoxur, a carbamate pesticide, is commonly used to manage household and agricultural pests. Despite its effectiveness in pest control, exposure to propoxur has been shown to induce various toxic effects, including liver damage, neurotoxicity, and oxidative stress[1]. The liver, as a primary organ responsible for detoxification, is particularly vulnerable to the toxic effects of propoxur, which can lead to severe hepatic dysfunction. Given the increasing use of propoxur and other pesticides, understanding the mechanisms underlying its hepatotoxicity is crucial for developing effective protective strategies[1].

Propoxur's toxicity is primarily attributed to its ability to inhibit cholinesterase, an enzyme critical for proper nerve function. This inhibition disrupts neurotransmission, leading to neurotoxic effects, but it also affects other organs, particularly the liver, where the detoxification of xenobiotics occurs. When exposed to propoxur, the liver experiences a series of biochemical and structural changes, including an increase in the levels of liver enzymes such as alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST). Elevated levels of these enzymes are indicative of hepatocellular damage and are commonly used as biomarkers for liver injury[2]. Furthermore, oxidative stress plays a pivotal role in the pathogenesis of liver injury caused by propoxur. Propoxur exposure leads to the generation of reactive oxygen species (ROS), which overwhelm the liver's antioxidant defense mechanisms, resulting in lipid peroxidation, DNA damage, and mitochondrial dysfunction[3]. The accumulation of ROS also triggers the activation of inflammatory pathways, contributing to further hepatic injury. Inflammatory cytokines such as interleukin-6 (IL-6) are released in response to oxidative stress, amplifying the damage and impairing the liver's ability to regenerate[4].

In light of these detrimental effects, there has been growing interest in identifying natural compounds with potential hepatoprotective properties. Lycopene, a carotenoid found in tomatoes, watermelon, and other red fruits, has emerged as a promising candidate due to its powerful antioxidant and anti-inflammatory effects. Lycopene is known to scavenge free radicals, reduce oxidative stress, and modulate inflammatory pathways, all of which make it a potential therapeutic agent for protecting against liver injury. Studies have shown that lycopene can alleviate oxidative damage in various organs, including the liver, by enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase[5, 6]. Additionally, lycopene has been found to suppress the production of pro-inflammatory cytokines, such as IL-6, which are implicated in the progression of liver damage[7].

The protective effects of lycopene against liver injury have been investigated in several experimental models, particularly in the context of hepatotoxicity induced by chemicals and toxins. Lycopene's ability to modulate the xanthine oxidase/uric acid signaling pathway, a crucial pathway in oxidative stress and inflammation, further supports its potential therapeutic application[8]. Xanthine oxidase is an enzyme that generates ROS and contributes to the inflammatory response, and its inhibition by lycopene may help reduce oxidative damage and inflammation in the liver. Furthermore, lycopene has been shown to improve liver function by reducing the levels of liver enzymes such as ALP, ALT, and AST, which are commonly used as markers of liver injury[8]. Given its antioxidant, anti-inflammatory, and liver-protective properties, lycopene presents a promising adjunct in mitigating the toxic effects of propoxur.

This study aims to explore the protective effects of lycopene against propoxur-induced liver injury in Wistar rats. Specifically, the study will focus on evaluating the modulation of oxidative stress markers, liver enzyme levels, in response to lycopene administration. By investigating the mechanisms through which lycopene mitigates propoxur-induced liver damage, this research may provide valuable insights into the development of novel therapeutic strategies for preventing pesticide-induced hepatotoxicity. Moreover, this study could contribute to the broader understanding of how natural compounds can be used to combat environmental toxin-induced organ damage, with potential implications for human health.

MATERIALS AND METHOD

Procurement of Compounds and Animals

All compounds used (Propoxur and lycopene) were procured from Adebayo Ige and Sons, Osogbo and verified at Pharmacology Department, University of Ilorin, Ilorin. Experimental animals used for this research were procured from the Animal Holdings College of Health Science, Osun State University, Osogbo. The animals were allowed access to food and ad libitum. They were given two weeks to get used to the lab condition before the study started. The study followed the rules set by the Health Research Ethics Committee at the College of Health Sciences, University of Ilorin, Ilorin, Nigeria, and complied with the National Institute of Health guidelines for caring for and using lab animals.

Experimental Design

A total number of thirty male Wistar rats, with an average weight of 165g, were used in the study. The rats were randomly divided into six groups (A, B, C, D, E, and F), each consisting of five rats. Group A served as the control. Group B was exposed to Propoxur for 5 minutes at 3 ppm for 30 days. Group C was exposed to Propoxur for 1 hour at 3 ppm for 30 days. Group D received Lycopene at 10 mg/kg for 30 days. Group E was exposed to Propoxur for 5 minutes at 3 ppm and received Lycopene at 10 mg/kg for 30 days. Group F was exposed to Propoxur for 1 hour at 3 ppm and received Lycopene at 10 mg/kg for 30 days. All treatments were administered orally.

Sacrifice of Experimental Animals, Sample Collection and Hormonal Assay

Blood was withdrawn from the apex of the heart (left ventricle) of the thirty male adult wistar rats, which were first anesthetized with 80 mg/kg of ketamine hydrochloride, 12 hours after the last administration just according to Saha *et al.,* 2005[9]. The blood was then dispensed into red-topped tubes for hormonal analysis. The liver was excised following an abdominal incision, and they were fixed in Neutral buffer Formalin for histological analysis. It was then dehydrated progressively in stronger alcohols, cleared in Xylene and infiltrated in paraffin wax, before being embedded in molten paraffin wax. A rotary microtome was then used to slice the paraffin block containing the tissue into 4 μm thick sections. The sections were then transferred to a glass slide, floated in a water bath set at 40 degrees Celsius, and stained with hematoxylin and eosin dyes

Hormonal Assay

Serum samples were assayed for MDA, Interleukin in batches with the control sera at both physiological and pathological levels by the standard Quantitative Enzyme-Linked Immunosorbent Assay (ELISA) technique with microwell kit which was manufactured by Syngenemed. The manufacturer instructions that accompanied the assay kits were strictly adhered to.

Measurement of Body Weight

The weights of the animals were obtained upon arrival and on weekly basis using digital weighing balance scale in order to account for possible results in physical changes in rats upon administration (Propoxur and Lycopene) at regular intervals. The weights are checked for the comparison of possible changes from the initial weight and kept in record.

STATISTICAL ANALYSIS

The mean and standard error of mean (S.E.M) of all data were calculated. Comparison of means was made by one way analysis of variance (ANOVA) using Graphpad Prism 8. Tukey's test was used to adjust for multiple comparisons. P value < 0.05 was considered to be statistically significant.

PCSK-9 Assay

Plasma proprotein convertase subtilisin/ kexin type 9 (PCSK-9) levels were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (manufacturer details). The assay was performed according to the manufacturer's instructions, and absorbance was recorded at 450 nm using a microplate reader (Zhao et al., 2021)[10].

Liver Enzyme Assays (ALT, AST, GGT)

The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) were determined using colorimetric spectrophotometric methods with commercially available diagnostic kits (manufacturer details). Enzyme activity was measured at specific wavelengths using a spectrophotometer, following the procedure described by Reitman and Frankel (1957)[11] for ALT and AST and Szasz (1969)[12] for GGT.

Lipid Peroxidation (MDA Assay) and Glutathione Peroxidase (GPx) Activity

The extent of lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels using the thiobarbituric acid reactive substances (TBARS) assay (Ohkawa et al., 1979)[13]. Briefly, liver homogenates were reacted with thiobarbituric acid (TBA) at 95°C for 60 minutes, and the absorbance of the resulting pink chromogen was measured at 532 nm.

GPx activity was determined using a coupled enzyme assay based on the oxidation of reduced glutathione (GSH) in the presence of hydrogen peroxide (H_2O_2). The decrease in absorbance at 340 nm due to the oxidation of NADPH to $NADP^+$ was monitored spectrophotometrically, following the method of Paglia and Valentine (1967)[14].

RESULTS

BIOCHEMICAL RESULTS

Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells

The results in Figure 1 show that Propoxur exposure increases NF-kB levels in a time dependent manner, which indicates inflammatory response. Lycopene alone does not induce inflammation and when co-administered with Propoxur reduces NF-kB levels compared to Propoxur only groups. This showed that lycopene has protective, anti-inflammatory effects against Propoxur induced toxicity.

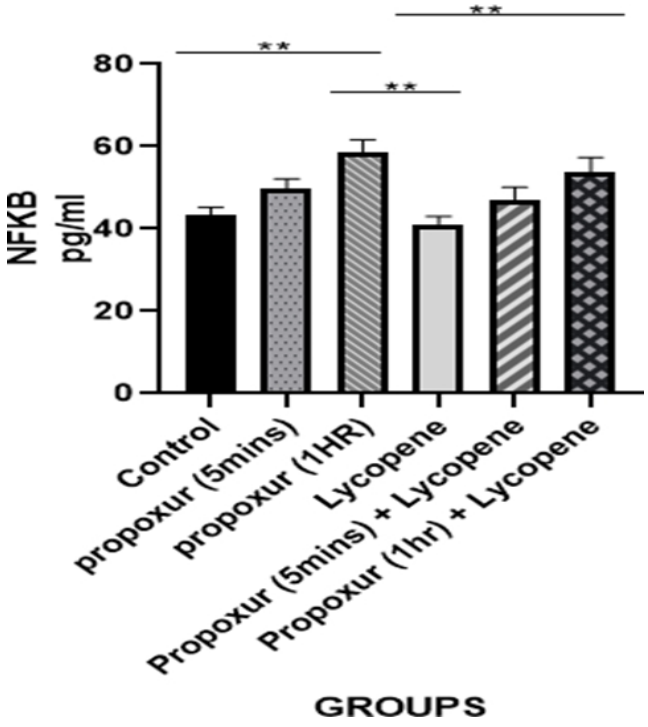

Figure 1: NFKB Analysis among the Groups

Alkaline phosphatase (ALP)

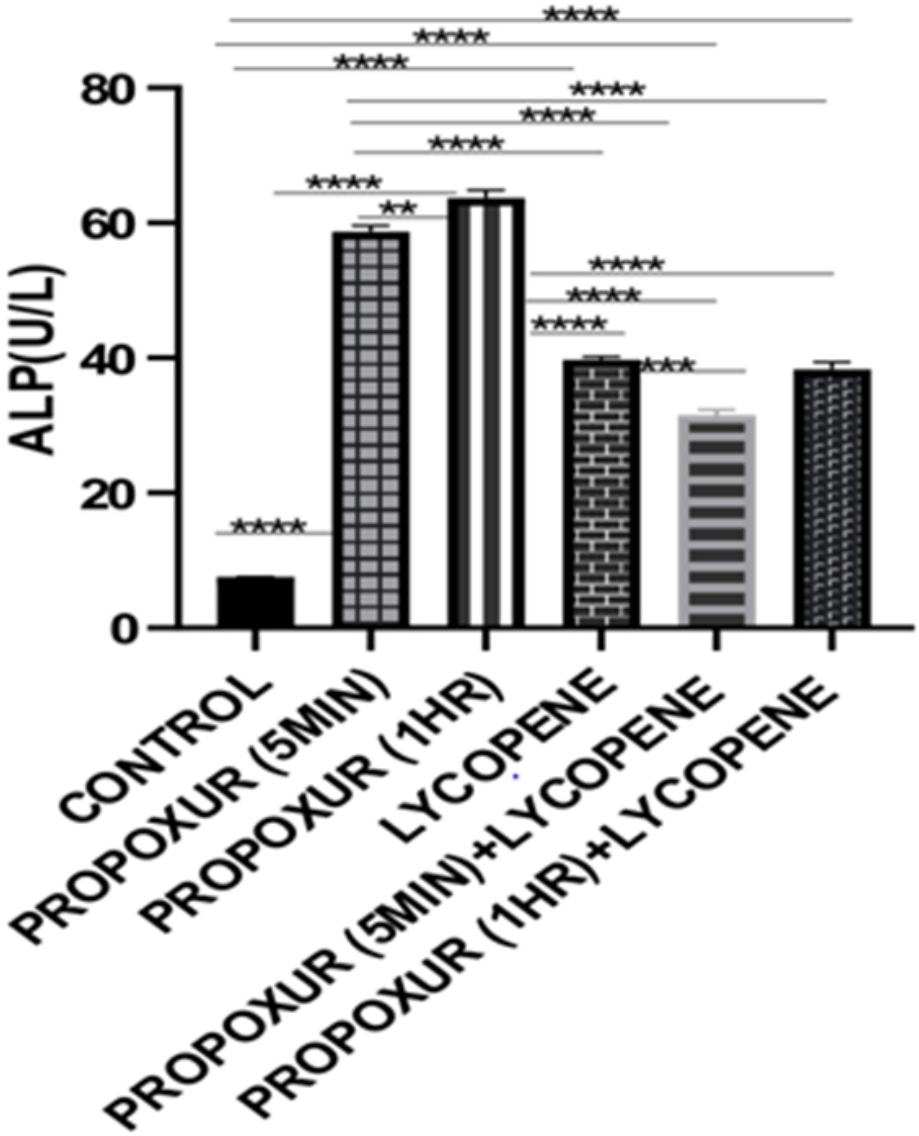

Figure 2: Alkaline phosphatase Activity across the Experimental Groups

The results in Figure 2 show that Propoxur exposure significantly increases ALP activity in a time-dependent manner, indicating liver damage. Lycopene alone does not affect ALP levels and when combined with Propoxur, it reduces ALP activity compared to Propoxur only group.

Aspartate Aminotransferase (AST)

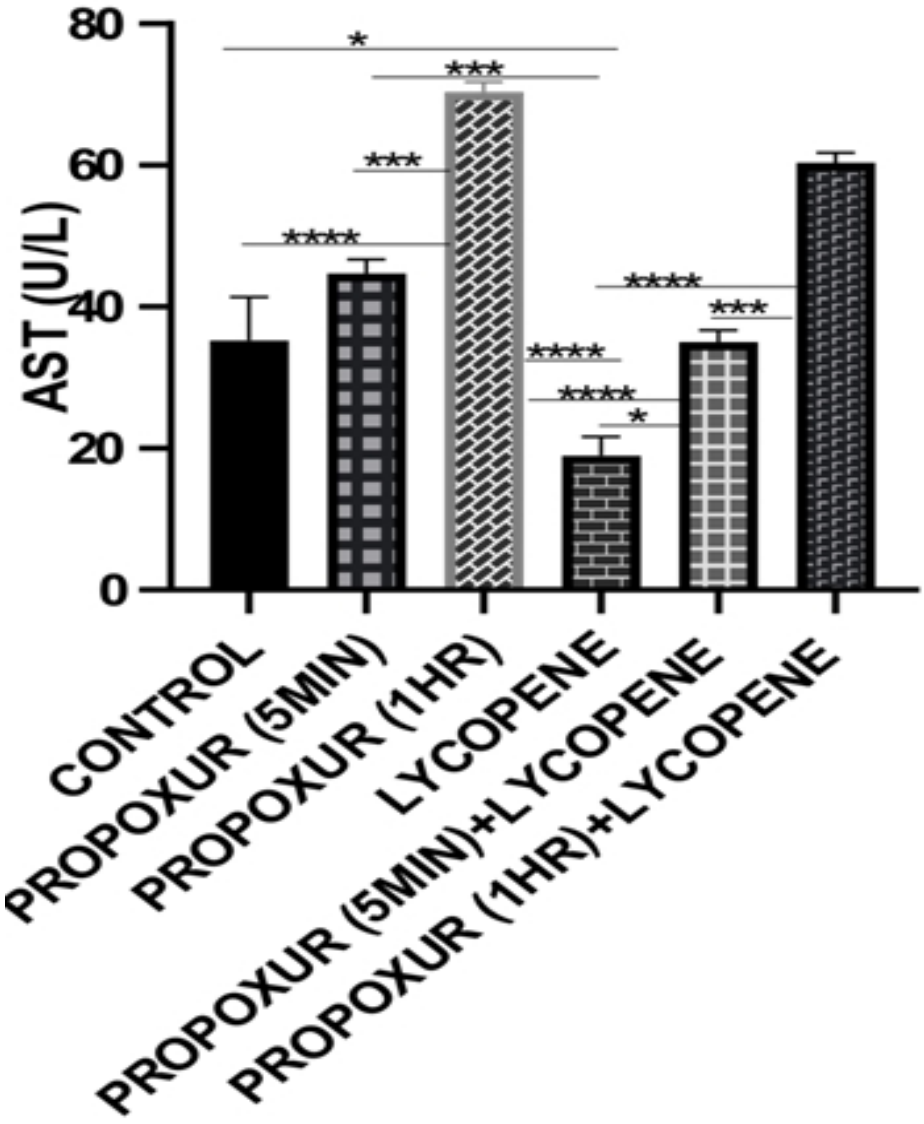

Figure 3: Level of Aspartate amino transferase (AST) Activity across Different Experimental Groups

The results in Figure 3 show that Prepoxur exposure significantly increases AST activity in a time dependent manner, indicating liver damage. Lycopene alone does not affect AST levels and when combined with Prepoxur, it reduces AST activity compared to Prepoxur only groups.

OXIDATIVE STRESS PARAMETERS

Malondialdehyde(MDA)

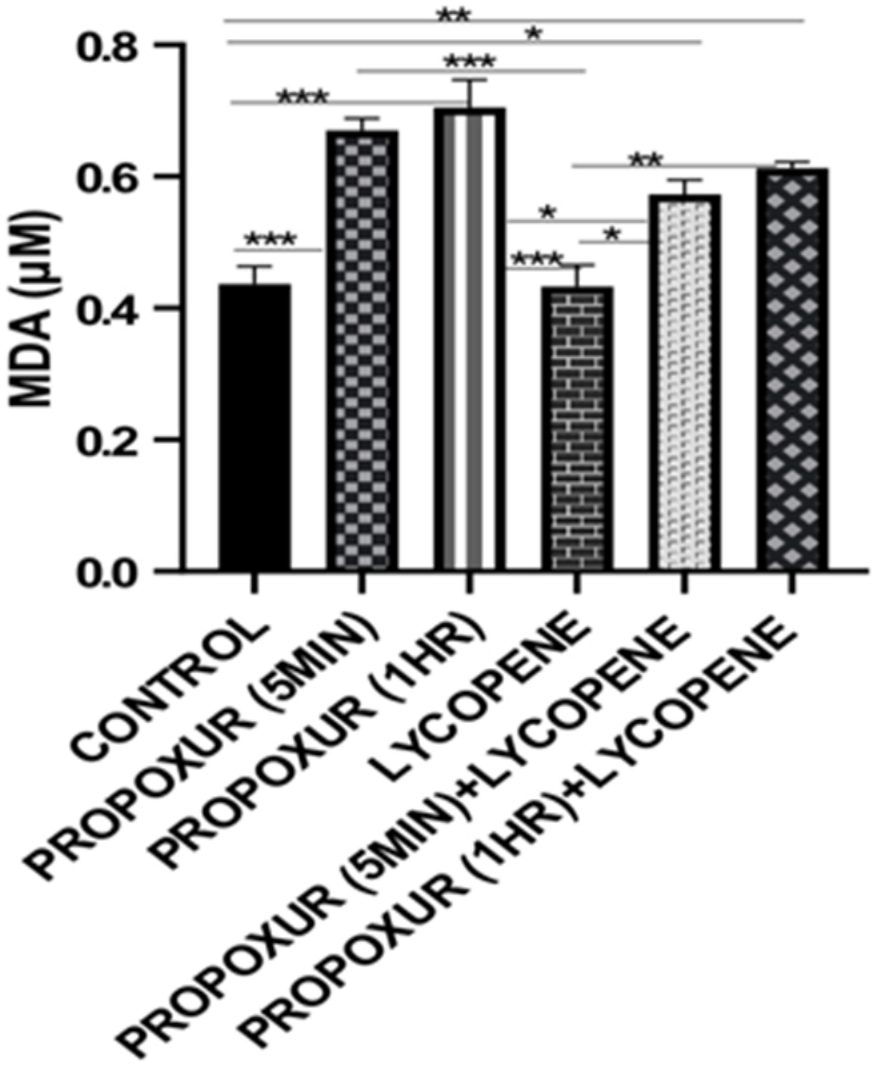

Figure 4: Level of MDA across the Experimental Groups

The results in Figure 4 show that Propoxur exposure significantly increases oxidative stress, as indicated by elevated MDA levels. However, Lycopene reduces these elevated MDA levels.

All data are represented as Mean ± SEM

P <0.05.(*=p<0.01,**=p<0.005,***=p<0.001).

Reactive Oxygen Species (ROS)

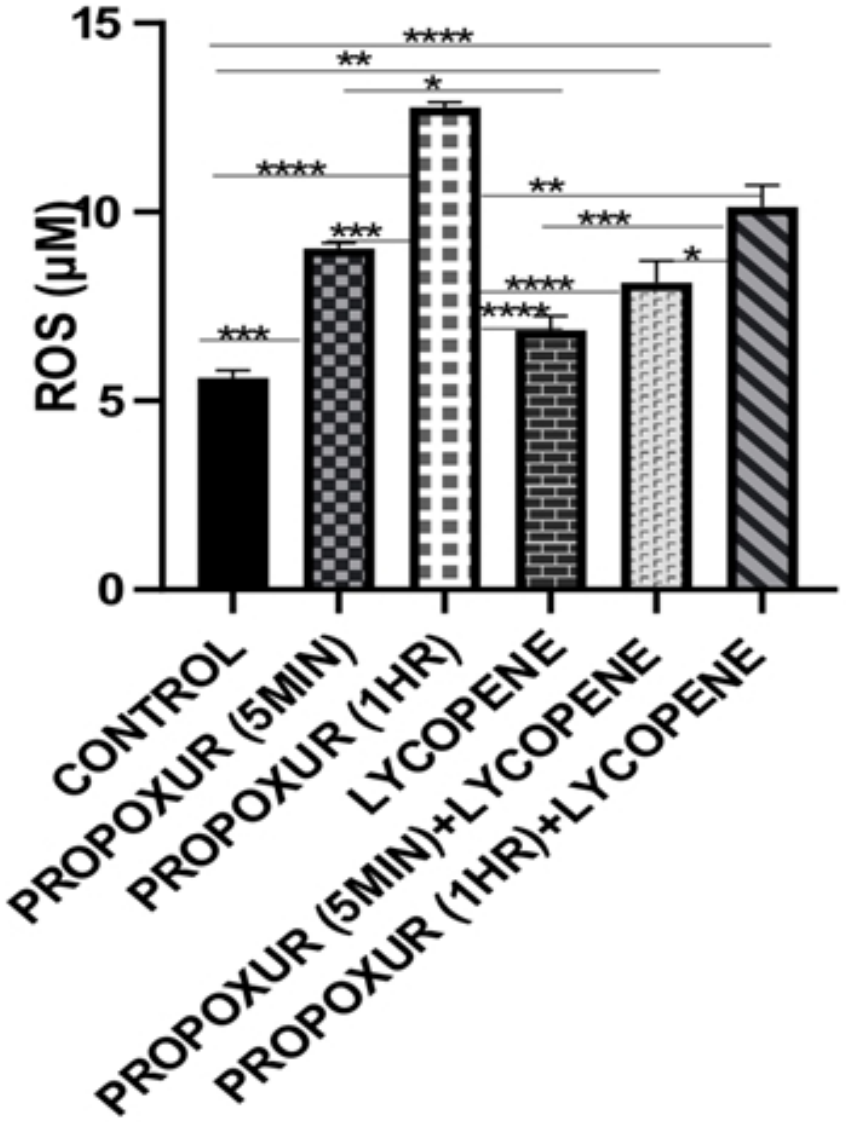

Figure 5: Level of ROS across the Experimental Groups

The results in Figure 5 show that Propoxur exposure significantly increases ROS levels, with higher levels observed after prolonged exposure (1 hour). However, Lycopene reduces these ROS levels.

All data are represented as Mean ± SEM

$p<0.05$.(*=$p<0.01$,**=$p<0.005$,***=$p<0.001$,****=$p<0.0001$).

Interleukin– 6 (IL– 6)

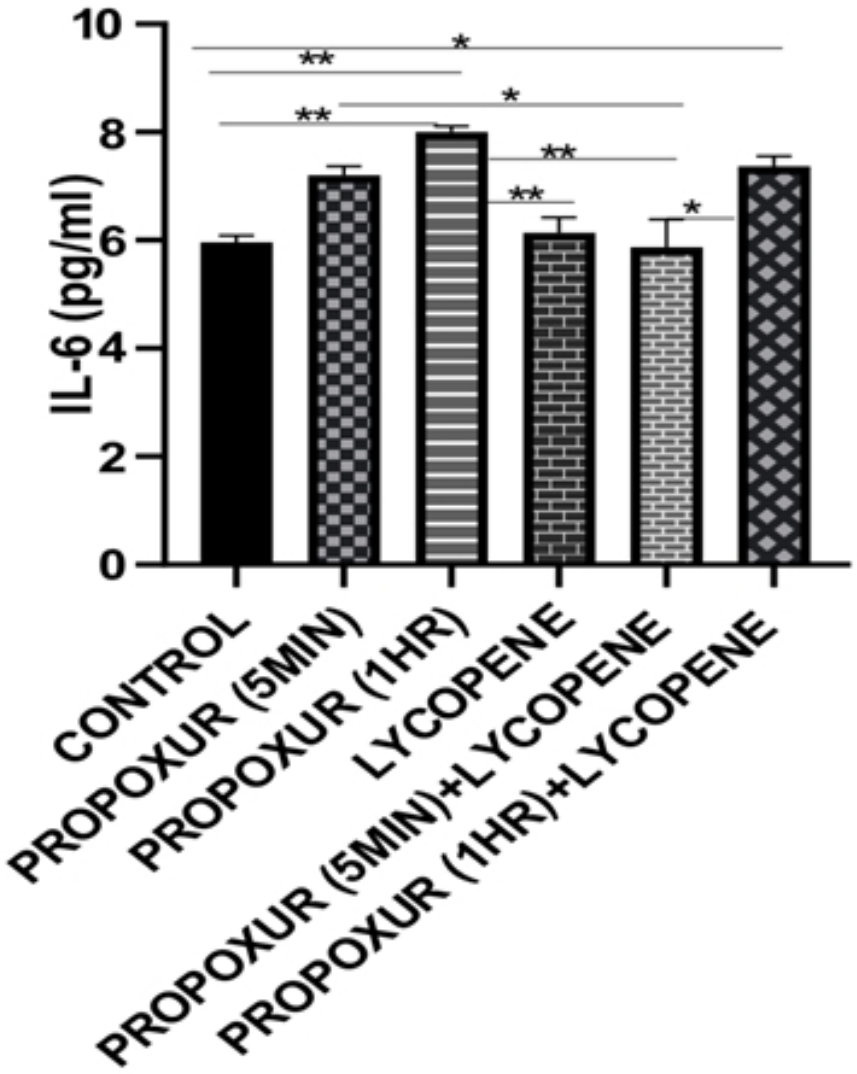

Figure 6: Level of IL-6 across all Experimental Levels

The results in Figure 6 show that Prepoxur exposure increases IL-6 levels indicating inflammation, with higher levels observed after prolonged exposure (1 hour). However, Lycopene reduces IL-6 levels.

All data are represented as Mean ± SEM

$p<0.05$. (*=$p<0.01$, **=$p<0.005$).

HISTOLOGICAL RESULTS

Representative photomicrographs of rat liver by light microscope with H&E staining atX200 magnification. Control liver showing normal hepatocytes arranged in cords, obvious sinusoids. Propoxur (5 mins) and Propoxur (1 hour) section showing degenerated hepatocytes, congested sinusoids, distorted hepatic tissue structure and collection of inflammatory cells. Lycopene treated rats showing similar architecture like the control. Propoxur (5minutes) + Lycopene, Propoxur (1hour) + Lycopene showed almost the normal appearance of hepatocytes around the central vein (CV) with few inflammatory cells.

Slim Arrow = Hepatocyte, CV = Central vein, Black Arrows = Inflammatory Cells

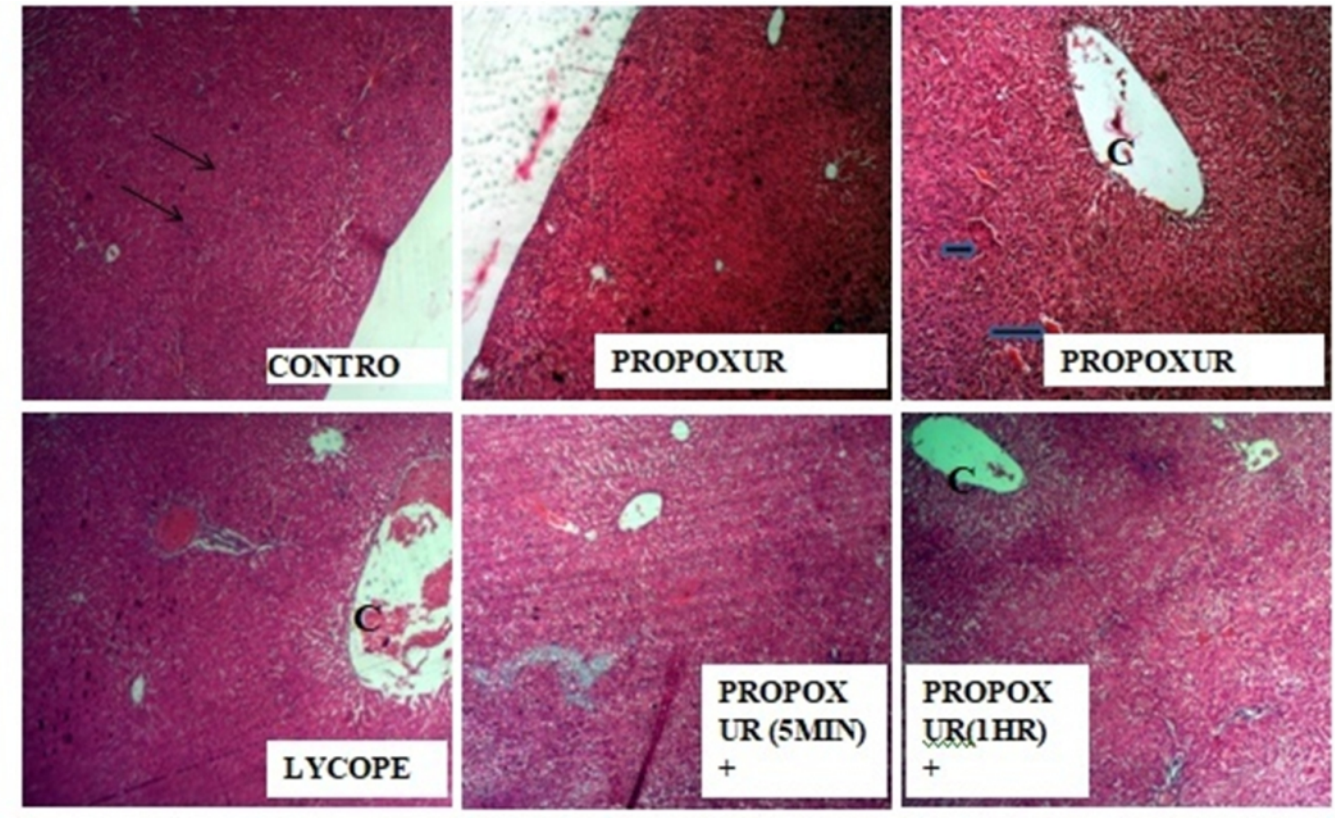

Figure 7: Photomicrograph of Histological Section of the Liver Stained with Hematoxylin and Eosin x200, done and arranged together using PowerPoint Software

DISCUSSION

The findings of this study provide critical insights into the protective effects of lycopene against propoxur-induced liver injury. Propoxur, a widely used carbamate pesticide, has been shown to cause significant hepatotoxicity through mechanisms involving oxidative stress, inflammation, and disruption of hepatic function. In this study, the administration of propoxur led to marked histological damage to the liver, evidenced by cellular degeneration and necrosis. These structural changes align with previous studies that have demonstrated the hepatotoxic potential of propoxur due to its ability to generate reactive oxygen species (ROS) and disrupt liver enzyme activity[2,3].

The observed increase in oxidative stress markers such as malondialdehyde (MDA) and ROS further supports the role of oxidative damage in propoxur-induced hepatotoxicity. The elevation of these markers indicates lipid peroxidation and a failure of the liver's antioxidant defense system, which is consistent with prior research (Rezaei *et al.,* 2019). Additionally, the elevated levels of liver enzymes, including alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST), confirm liver dysfunction, as these enzymes are commonly released into the bloodstream during hepatic injury[4]. The inflammatory response, marked by an increase in interleukin-6 (IL-6), highlights the role of inflammation in exacerbating liver damage caused by propoxur exposure.

However, the co-administration of lycopene significantly mitigated the adverse effects of propoxur. Lycopene, a potent antioxidant, reduced oxidative stress by scavenging free radicals and enhancing the activity of endogenous antioxidant enzymes. This is consistent with findings from earlier studies that reported the ability of lycopene to attenuate oxidative damage in various models of chemical-induced organ injury[5,7]. The reduction in MDA and ROS levels observed in this study suggests that lycopene effectively counteracts lipid peroxidation and oxidative stress, thereby protecting the liver from damage.

Furthermore, lycopene's anti-inflammatory properties were evident in the significant reduction of IL-6 levels in the treated groups. This aligns with previous research showing that lycopene can suppress the production of pro-inflammatory cytokines, thereby mitigating inflammation-associated liver injury[7]. The improvement in liver enzyme levels, along with the preservation of liver histology in lycopene-treated groups, underscores its hepatoprotective effects. These findings support the hypothesis that lycopene can modulate key pathways involved in oxidative stress and inflammation, such as the xanthine oxidase/ uric acid signaling pathway, to protect against liver injury[7,3]. The weight loss observed in rats exposed to propoxur alone is indicative of systemic toxicity, which could be attributed to the metabolic burden and stress induced by the pesticide. Lycopene administration not only reduced liver damage but also helped maintain body weight, suggesting its role in improving overall metabolic health and reducing systemic toxicity.

CONCLUSION

In conclusion, this study highlights the protective role of lycopene against propoxur-induced liver injury, primarily through the modulation of xanthine oxidase/uric acid signaling. Our findings underscore the potential of lycopene as a natural therapeutic agent in mitigating pesticide-induced oxidative stress and liver damage. This research contributes valuable insights into toxicology and antioxidant therapy, offering a basis for future studies and potential clinical applications.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Research Paper

Comparative Evaluation of Intra-oral Wound Healing with Silk Suture v/s. n-butyl-2-cyanoacrylate after Alveoloplasty

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ABSTRACT

***Background**:*

Effective crack check is a pivotal element of intraoral surgical procedures. While conventional non-absorbable sutures remain extensively used, indispensable styles similar as synthetic absorbable sutures, towel bonds, and surgical masses have gained adding acceptance in recent times. Among these, cyanoacrylate- grounded towel bonds have demonstrated notable biocompatibility and ease of operation. In order to promote intraoral crack mending after alveoloplasty, the current investigation compared the clinical concerns of 3-0 silk sutures and n-butyl-2-cyanoacrylate glue.

***Materials & Methods**:*

This prospective clinical trial was conducted on 20 cases taking bilateral alveoloplasty in the same dental bow (maxillary or mandibular). Individuals with previous oral diseases or systemic ails were excluded. In each case, one surgical point was closed using n- butyl-2-cyanoacrylate, while the contralateral point was secured with 3- 0 pleated silk sutures. Parameters estimated included time needed for crack check, achievement of intraoperative and postoperative haemostasis, interval before first deliverance analgesic input, postoperative pain intensity, and rate of crack mending.

***Results**:*

Closure with n- butyl-2-cyanoacrylate demonstrated superior haemostatic control, significantly reduced operative time, dropped postoperative pain, and faster crack mending compared to 3- 0 silk sutures.

***Conclusion**:*

Within the limitations of this study, n- butyl-2-cyanoacrylate can be considered a practical and effective volition to conventional silk sutures for intraoral crack check after alveoloplasty, offering bettered haemostasis, lesser patient comfort, and enhanced mending issues.

KEYWORDS: Cyanoacrylate, n-butyl-2-cyanoacrylate, Towel glue, Silk sutures, Alveoloplasty

INTRODUCTION

Preface Following any surgical procedure, icing proper crack check remains a matter of critical concern. Surgical injuries can be managed through various check ways; still, the primary objects remain constant — minimizing the trouble of infection, barring dead space, and precisely approaching crack peripheries to achieve optimal functional and aesthetic issues[1]. Crack mending progresses through four distinct and well-orchestrated phases haemostasis, inflammation, proliferation, and redoing. For successful recovery, these stages must do in the correct sequence and within applicable time frames[2].

Any disturbance or detention in one or further of these phases can vitiate healing. Prompt and secure check is therefore essential to avoid complications and promote smooth, uneventful recovery. Over the times, literature has proved a range of crack check styles, from traditional non-absorbable sutures to advanced options analogous as synthetic absorbable sutures, surgical millions, and kerchief bonds[3,4].

Despite their wide use, conventional suturing ways have notable limitations, including kerchief trauma, advanced trouble of postoperative infection, the need for original anaesthesia, longer procedure time, implicit needle- stick injuries to the motorist, and the demand for a fresh visit to remove sutures[5]. Cyanoacrylates, first synthesized by Ardis in 1949, are presto-acting bonds that polymerize within seconds upon contact with protein-rich shells, forming strong yet flexible bonds[6].

These parcels make them precious in a variety of surgical operations, including crack check, haemostasis, skin graft preoccupation, and other operative procedures[7]. Different types of cyanoacrylates are available — methyl, ethyl, n- butyl, isoamyl, isohexyl, and octyl — classified according to the length and complexity of their carbon chains[4]. Still, their limitations include fairly low tensile strength (making them incongruous for high-pressure injuries) and reduced effectiveness in wettish, disunion-prone areas analogous as the hands and bases. They are also contraindicated in cases with known perceptivity to formaldehyde or cyanoacrylate, those who are immunocompromised, and in the presence of infected injuries.

In light of these considerations, the present study was accepted to estimate and compare the clinical performance of two generally used paraphernalia — n-butyl-2-cyanoacrylate and silk sutures (Mersilk) for intraoral crack check in cases witnessing alveoloplasty.

A further end was to determine whether these paraphernalia could reduce operative time and minimize the frequency of postoperative follow-up visits.

MATERIALS AND METHODS

This study was carried out from May 2023 to November 2024 in the Pacific Dental College and Research Centre's Department of Oral and Maxillofacial Surgery in Udaipur.

It included 20 patients who required bilateral alveoloplasty in which one side 3-0 silk suture (Mersilk) were placed and on contralateral side n- butyl-2-cyanoacrylate were placed.

The 20 samples were divided into 2 groups as follows: Group I 3-0 silk suture (Mersilk) Group II N- butyl-2-cyanoacrylate in the same patient.

INCLUSION CRITERIA

- Both the male & female of age 18 years & above
- Patient with bilateral edentulous arches (Both in Maxillary & Mandibular arch) required Alveoloplasty

EXCLUSION CRITERIA

- Patient with any pre-existing pathology (oral cavity)
- Patient with systemic conditions including anaemia or diabetes

METHODOLOGY

All participants underwent through detailed case history, clinical examinations, standardized digital radiograph, and clinical photographs. A thorough clinical examination including both hard and soft tissue examinations were carried out.

Crestal incision was placed on alveolar mucosa. Mucoperiosteal flap was reflected as required and bony spicule or prominence was removed using bone rongeur and round bur. Smoothening of the arch was done using bone file. All procedure was carried out under local anaesthesia.

Group I used 3-0 silk suture (Mersilk) to close the flap, while Group II used n-butyl-2-cyanoacrylate.

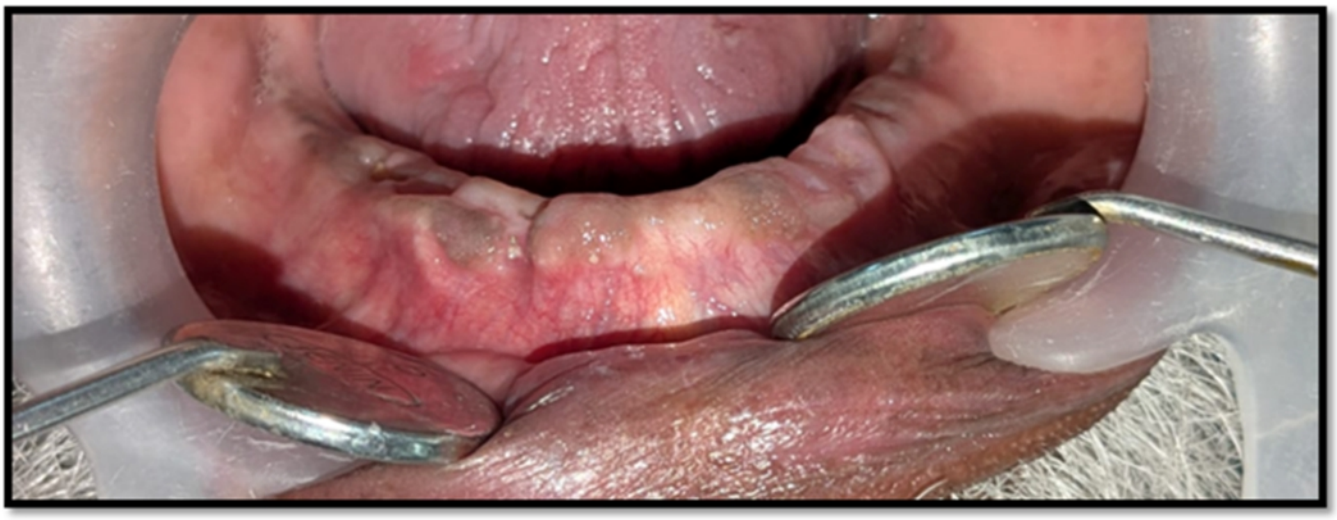

Figure 1: Pre-operative

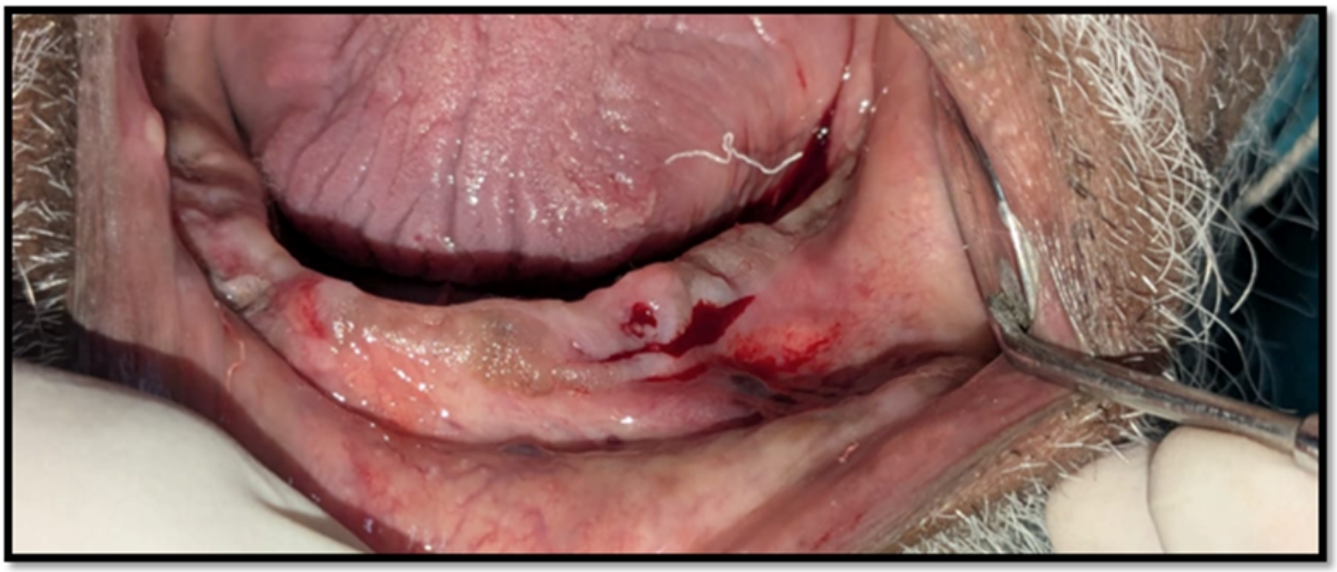

Figure 2(A): Intra-operative Group A (Incision Placed)

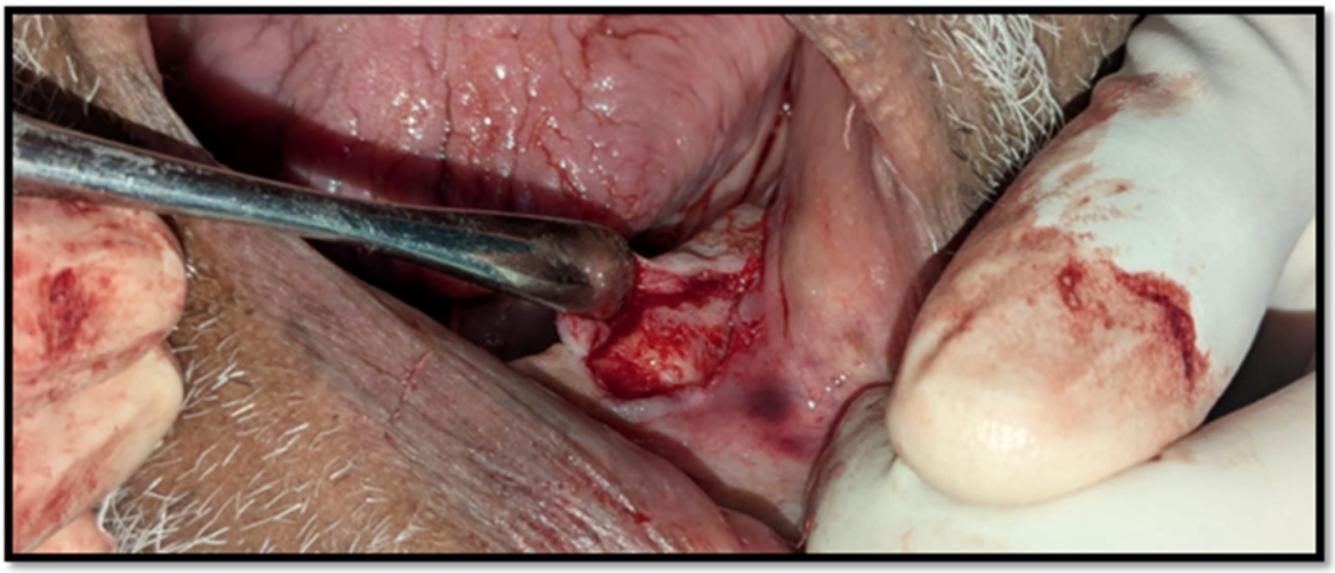

Figure 2(B): Intra-operative Group A (Bony Spicule Removed)

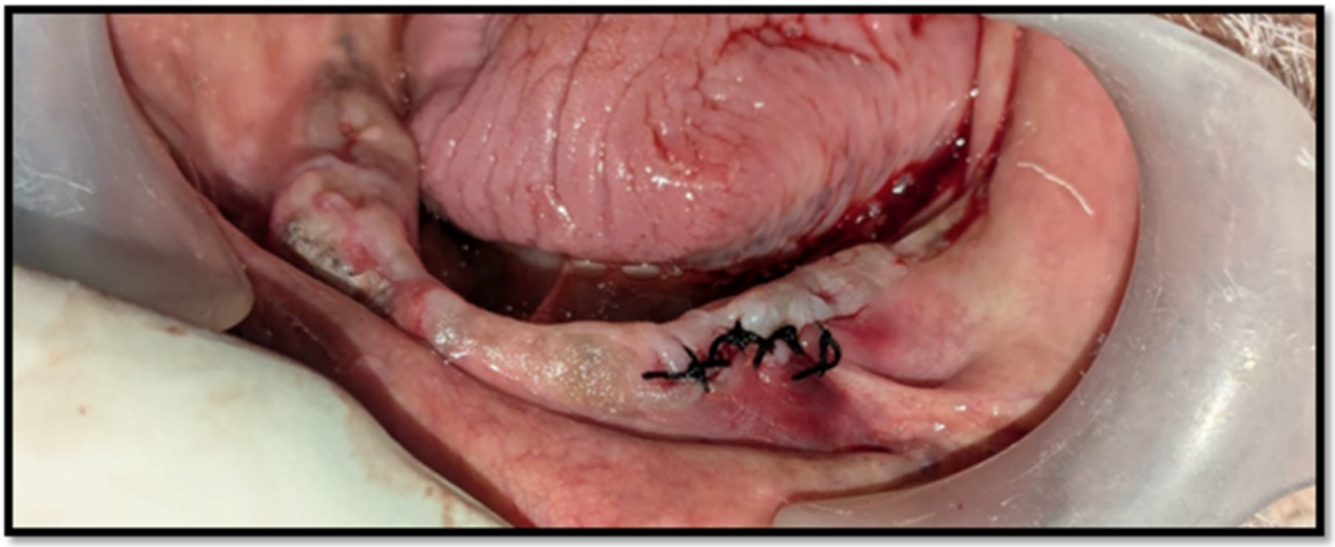

Figure 2 (C): Intra-operative Group A (Closure Done using Silk Suture - Mersilk)

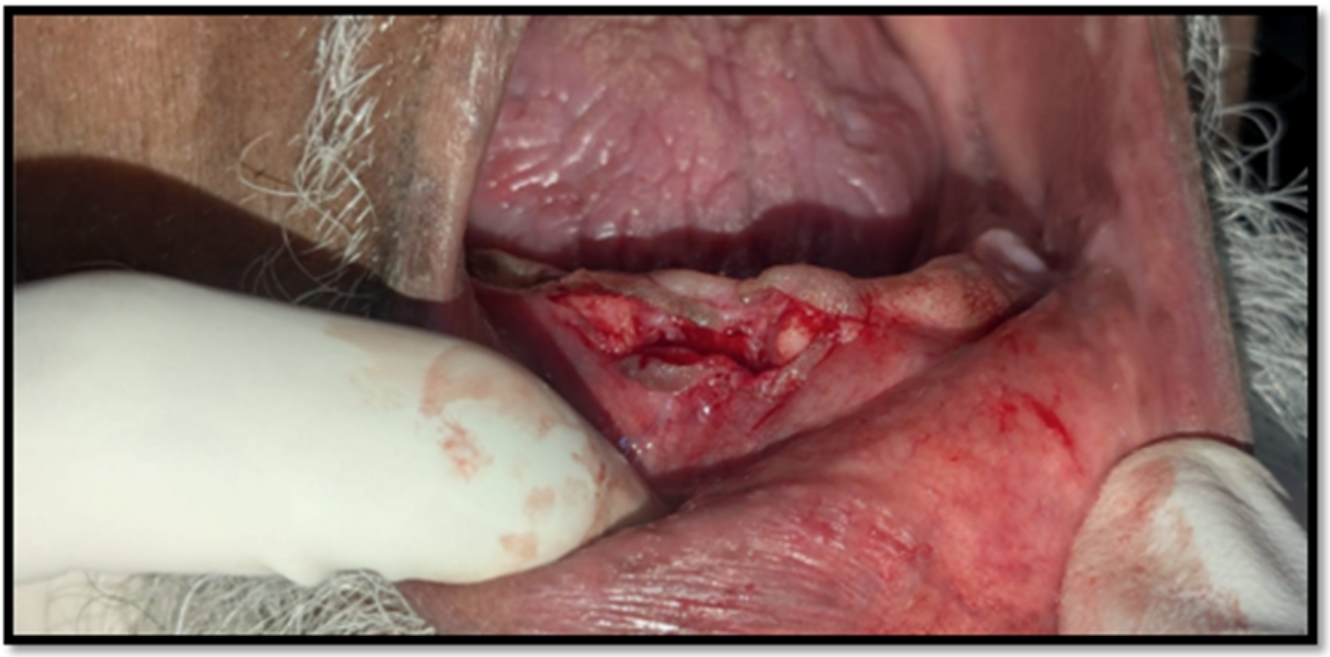

Figure 3(A): Intra-operative Group B (Incision Placed)

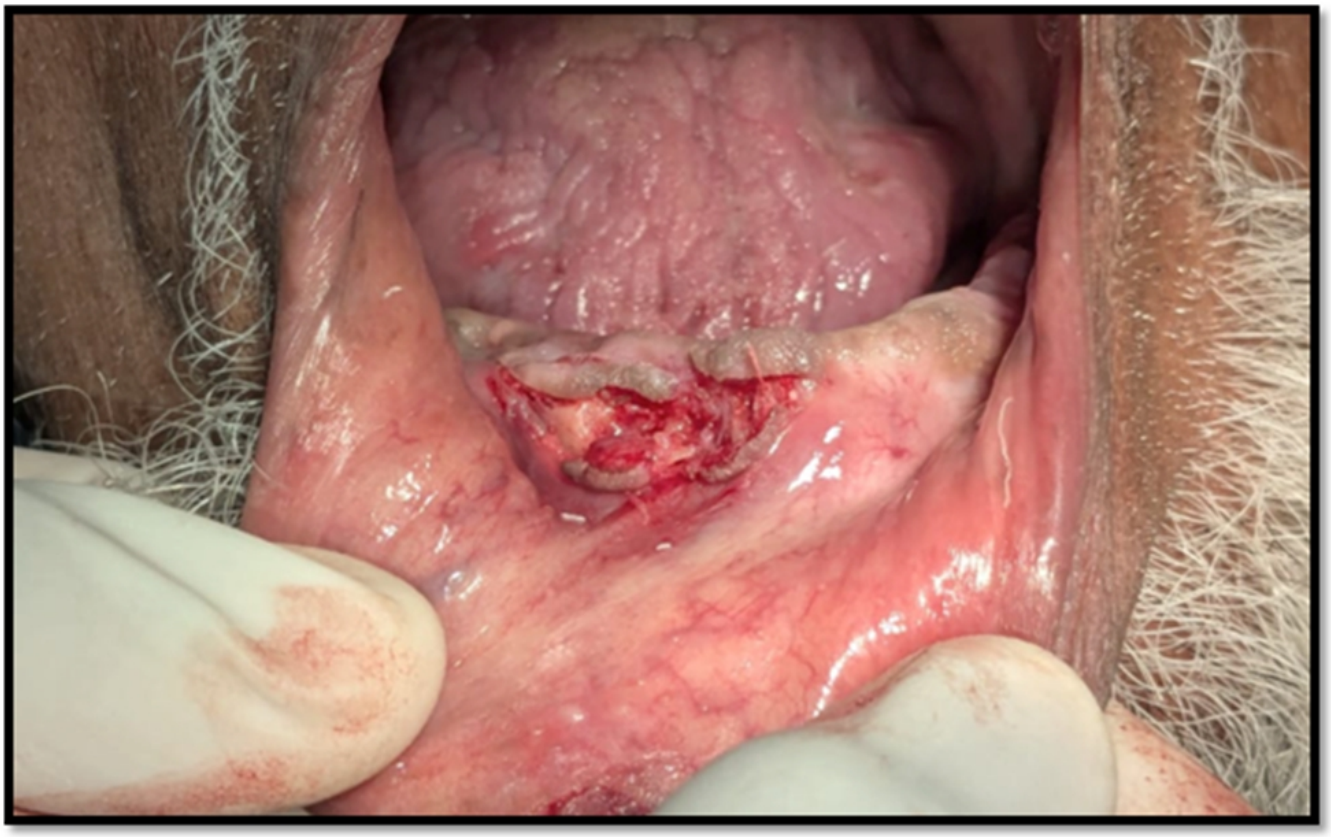

Figure 3(B): Intra-operative Group B (Bony Spicule Removed)

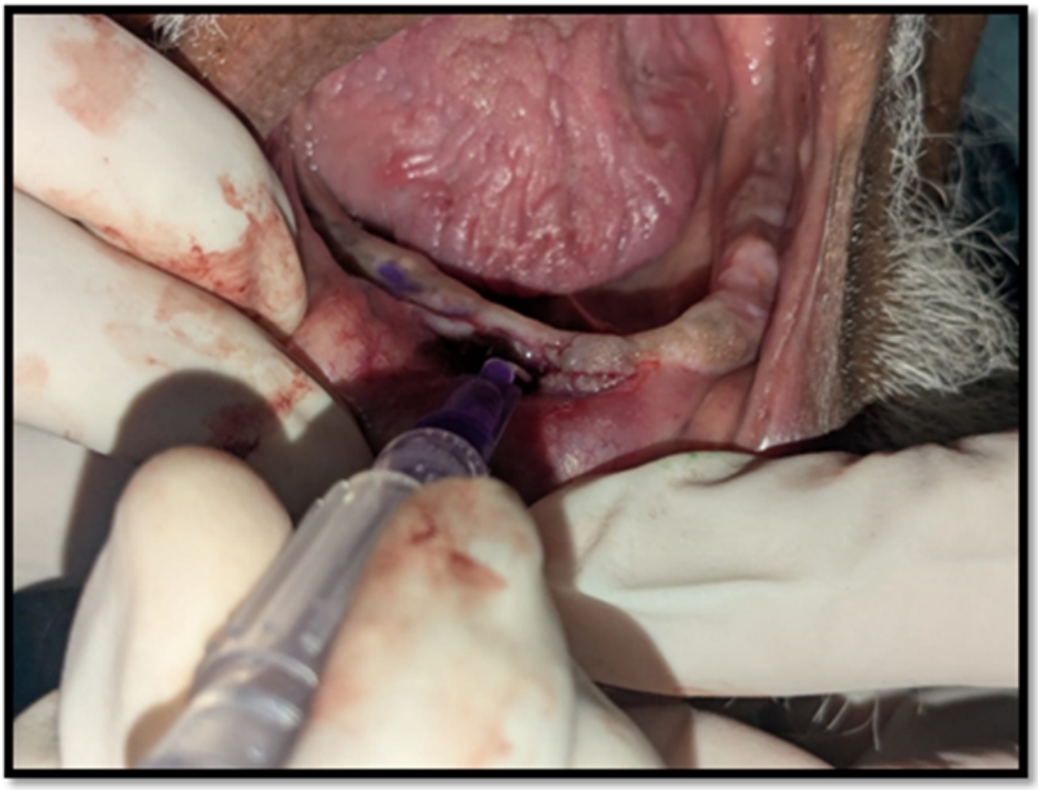

Figure 3 (C): Intra-operative Group B (Placing n-butyl 2-cyanoacrylate)

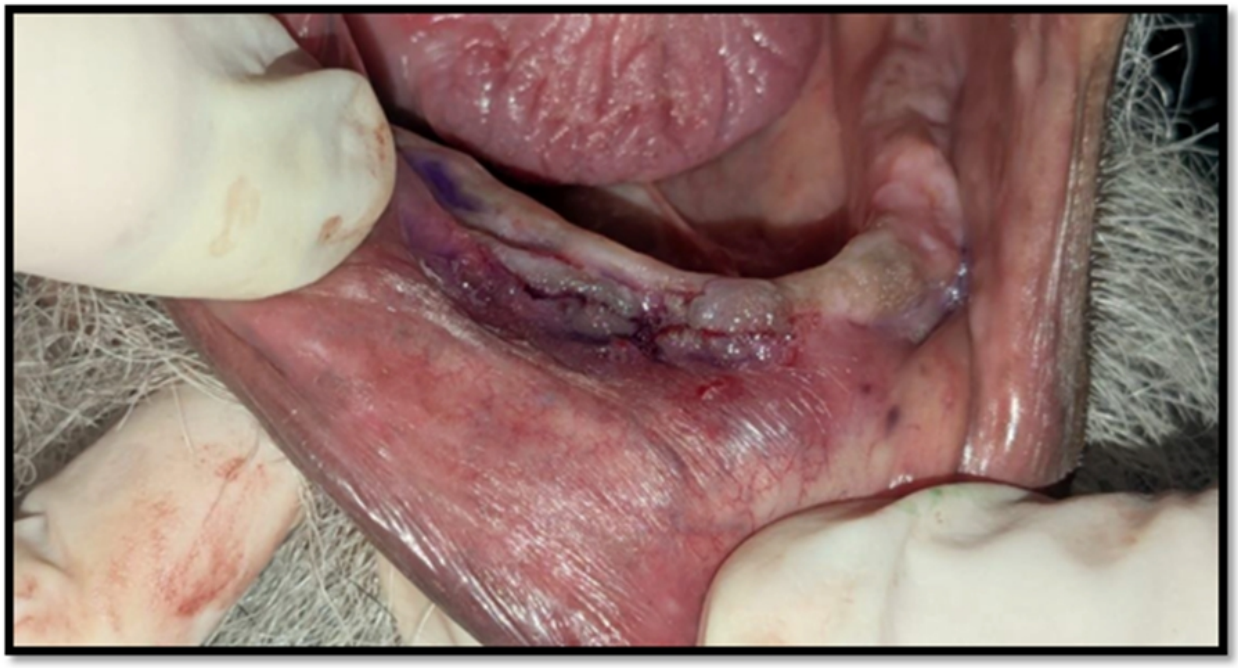

Figure 3 (D): Intra-operative Group B (Closer Done using n-butyl 2-cyanoacrylate)

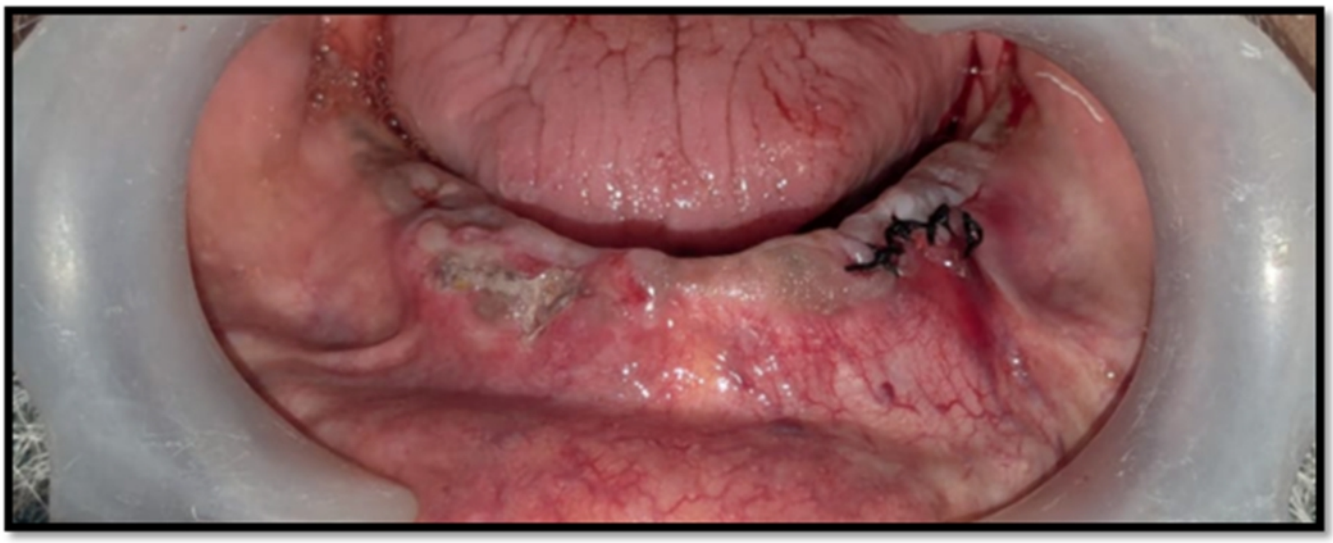

Figure 4: Post-operative

RESULTS

Data analysis was performed using IBM SPSS Statistics software(interpretation 22.0; IBM Corp., Armonk, NY, USA). A statistically significant p-value was defined as less than 0.05.

Males made up 55% of the participants, while females made up 45%. The mean age of the study population was 62 years, with ages ranging from 40 to 80 years.

Out of the 20 patients enrolled, 2 individuals (10%) fell within the 40–49-year age range, 7 patients (35%) were between 50–59 years, another 7 patients (35%) were in the 60–69-year range, and 4 patients (20%) were aged between 70–80 years.

The average time needed for crack check in Group 1 was 3.77 ± 1.11 twinkles, compared with 0.91 ± 0.37 twinkles in Group 2. This resulted in a mean difference of 2.86 minutes ($p < 0.001$) [Table 1].

Group 1 took a normal of 2.71 ± 1.11 twinkles to reach hemostasis, whereas Group 2 took a normal of 0.44 ± 0.23 twinkles, with a mean difference of 2.26 twinkles ($P< 0.001$).

Group I had 41.2 of cases without discomfort, whereas Group II had 58.8. On the other hand, the prevalence of discomfort was 43.5 in Group II and 56.5 in Group II($\chi 2 = 0.921$, $P = 0.337$) [Table 2].

Table 1: Comparing the time (min.) to achieve wound closure

	GROUP	NO. OF PATIENTS	MEAN	SD	T (Min.)	P-VALUE	MEAN DIFFERENCE
TIME TO	I	20	3.770	1.1108	10.917	< 0.001	2.8600
WOUND CLOSURE	II	20	0.910	0.3726			

Table 2: Comparison of post operative pain in Group I and Group II

TIME INTERVAL	GROUP	MEAN	N	STD. DEVIATION	STD. ERROR MEAN	P VALUE
1ST DAY	Silk suture (Group 1)	5.960	20	2.030	0.287	0.001
	n-butyl-2-cyanoacrylate (Group 2)	3.280	20	1.796	0.254	
7TH DAY	Silk suture (Group 1)	5.220	20	1.556	0.220	0.002
	n-butyl-2-cyanoacrylate (Group 2)	2.420	20	1.052	0.149	

Group I and Group II had mean rank values of 18.50 and 22.50 for postoperative wound healing, respectively (Mann–Whitney U value = 160.00, P = 0.28). Both groups' wound healing was evaluated on the first and seventh days.

Crack mending was assessed on base of Landry, Turnbull, and Howley indicator. On 1st day in Group I, 02 patients had excellent healing 4 patients had very good healing 6 patients had good healing 4 patients had poor healing while 4 had very poor healing. In Group II, 7 patients had excellent healing while 5 patients had very good healing while 3 patients had good healing while 2 patients had poor healing while 3 patients had very poor healing [Table 3].

There was a statistically significant difference of 0.002 between the groups.

Table 3: Comparison of post-operative wound healing on 1st day in Group 1 & Group Il

GROUPS			FIRST DAY WHI					TOTAL	CHI SQUARE	P VALUE
			1	2	3	4	5			
I	Silk suture	Count	2	4	6	4	4	20	16.72	0.002
		%	10%	20%	30%	20%	20%	100%		
II	N-butyl-2-cyanoacrylate	Count	7	5	3	2	3	20		
		%	35%	25%	15%	10%	15%	100%		

{WHI- Wound Healing Index}

On 7th day in Group I, 3 patients had excellent healing 06 patients had very good healing 04 patients had good healing 05 patients had poor healing while 02 had very poor healing.

In Group II, 9 patients had excellent healing while 06 patient had very good healing while 03 patients had good healing while 01 patients had poor healing while 01 patient had very poor healing [Table 4].

There was a statistically significant difference of 0.010 between the groups.

Table 4: Comparison of post operative wound healing on 7th day in Group I & Group II

GROUPS			SEVENTH DAY WHI					TOTAL	CHI SQUARE	P VALUE
			1	2	3	4	5			
I	Silk suture	Count	3	6	4	5	2	20	22.165	0.010
		%	15%	30%	20%	25%	10%	100%		
II	N-butyl-2-cyanoacrylate	Count	9	6	3	1	1	20		
		%	45%	30%	15%	5%	5%	100%		

{WHI- wound healing index}

DISCUSSION

Restoring structural soft tissue support, lowering wound tension, and attaining everted skin margins are the main goals of wound closure principles. The most natural-looking appearance is achieved with accurate wound closure and precise approximation of the wound boundaries.

Suturing have been used as a prime module for treatment for various procedures for a long period of time. Various studies have been done of different types and methods of suturing. The advantage of suturing is ease of availability, technical ease etc. At the same it does carry some disadvantages like post operative infection, delayed healing and scar formation on extraoral site, difficult to perform in uncooperative patient or children or geriatric patients.

In surgery, tissue adhesives have been used to enhance wound healing, adhesion, and haemostasis. Collectively, these products fall into one of two categories: biologic or synthetic. In general, biologic glues fall into one of two categories: homologous or autologous. They are mostly fibrin adhesives. They have found widespread application as wound adhesion and internal tissue sealants. Autologous platelet adhesives may be more effective than fibrin glues at promoting wound healing[8].

To treat severe lacerations, bronchopleural fistulas, myocardial rips, mesh fixation for inguinal hernia surgery, cosmetic rhinoplasty, embolization of intracranial AV abnormalities, and CSF leaks, cyanoacrylates have been employed[9].

Adhesives play a very small role in oral and maxillofacial surgery; however, this is quickly changing. In 1949, Ardis discovered and manufactured chemical adhesives in 1949[5]. These tissue glues, which have been used to approximate skin, are mostly made from cyanoacrylate. When Coover finally disclosed their adhesive qualities in 1959, they were employed for the first time in humans[10,11]. With R standing for side chain, their usual formula is CNCH2=COO-R. Formaldehyde and a cyanoacrylate ester undergo reversible condensation to generate the monomer, which is what they belong to. In the presence of anions, particularly hydroxyl ions, these adhesives polymerize.

Mehta et al. Carried out one of the earliest investigations on the application of cyanoacrylate glue in dental procedures. The osteosynthesis of 10 mandibular fractures was carried out by the authors using butyl cyanoacrylate. They observed no negative side effects or chromosomal alterations in the patients throughout follow-up periods of one to six months[12].

The gene expression and mineralized tissue changes of autogenous grafts fixed with n-butyl-2-cyanoacrylate in the mandible of six rabbits were examined over a brief period of time (4–8 days) and contrasted with screw fixation. Advanced gamma-sterilized, nonpigmented, nontoxic, nonallergic, and biostatic tissue glue is isoamyl 2-cyanoacrylate. In addition to being easy to apply and exhibiting proven safety, it aids in quick wound closure with less scarring and lowers the risk of trauma and infection following surgery, resulting in efficient wound healing with little danger. In this study, tissue adhesives containing n-butyl-2-cyanoacrylate are used to compare the clinical healing, pain, and wound closure of intraoral wounds.

Qureshi A. et al[13] has shown that n-butyl-2-cyanoacrylate had bacteriostatic properties. Bhaskar et al. reported that local phagocytosis of butyl cyanoacrylate resulted in the formation of abscess and mild tissue necrosis[14]. Annabelle Rajaseharan

noted that neither n-butyl-2-cyanoacrylate nor isoamyl 2-cyanoacrylate tissue adhesives caused wound infections in any of his patients[15]. Rosin et al[16] revealed an instance of n-Butyl 2-cyanoacrylate-induced wound infection, which he linked to incorrect wound edge approximation.

When utilizing n-butyl-2-cyanoacrylate, the frequency of wound dehiscence has been reported in several investigations. Qureshi et al revealed two out of 102 instances of partial dehiscence during laparoscopic and general procedures, and he linked this occurrence to the insufficient drying of the skin's margins prior to the adhesive's application.

The findings of our study are consistent with that of Mehta et al[12], Qureshi A et al[13], Bhaskar et al[14], Annabelle Rajaseharan, Qureshi et al[14]; stating that cyanoacrylate is more favourable than silk suture in the intraoral closure of tissues in alveoloplasty.

CONCLUSION

Following alveoloplasty, wound closure can be effectively achieved using cyanoacrylate adhesive. In our study, when compared to silk suturing, the adhesive demonstrated superior haemostatic properties, reduced postoperative pain and swelling, and shortened operative time. Additionally, wound healing outcomes were more favourable with the adhesive than with conventional sutures.

The technique was also well-received by the operating surgeon. Owing to its bacteriostatic nature, cyanoacrylate offers added protection against wound infection. Other notable advantages include ease of application, faster procedure completion, and elimination of the need for a follow-up visit for suture removal. The primary drawback observed was the higher cost of the adhesive.

Further prospective research is warranted to confirm these findings and to evaluate the overall cost-effectiveness of tissue adhesives compared to surgical sutures, particularly in low-tension elective procedures. Nevertheless, our results indicate that cyanoacrylate adhesive is a superior alternative to traditional silk suturing for wound closure following alveoloplasty.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Review

Pre-Exposure Prophylaxis for HIV: Emerging Role of Lenacapavir – A Comprehensive Review

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ABSTRACT

HIV continues to pose a substantial public health burden, with over 1.3 million new cases globally in 2023. Pre-exposure prophylaxis (PrEP) has transformed the HIV prevention landscape. However, oral PrEP regimens suffer from adherence challenges, resistance, and stigma. The 2025 FDA approval of Lenacapavir, a novel capsid inhibitor with biannual subcutaneous administration, introduces a promising long-acting PrEP option. This review provides a comprehensive appraisal of PrEP evolution, current regimens, the pharmacology and clinical efficacy of Lenacapavir, implementation barriers, and future directions, with a focus on its potential in the Indian context.

KEYWORDS: HIV, Pre-exposure prophylaxis, Lenacapavir

INTRODUCTION

Despite widespread ART rollout, HIV remains a pressing global concern, particularly in sub-Saharan Africa and Southeast Asia. India, with approximately 2.4 million people living with HIV, continues to witness transmission among key populations such as MSM, sex workers, and transgender individuals[1]. PrEP offers a biomedical shield against HIV, with studies showing a reduction in risk by up to 99% when taken consistently[2].

However, traditional oral PrEP regimens demand daily adherence, often challenging in real-world settings. Lenacapavir, the first-in-class HIV capsid inhibitor approved on 18 June 2025 for PrEP use, offers a long-acting alternative with subcutaneous administration every six months.

Evolution of HIV Pre-Exposure Prophylaxis

Historical Background

Initial evidence for PrEP emerged from macaque models and transitioned into human trials such as iPrEx (2010), which showed 44% risk reduction among MSM using TDF/FTC[3]. This led to FDA approval of TDF/FTC (Truvada) for PrEP in 2012. Subsequent trials (PROUD, IPERGAY, HPTN-083/084) validated PrEP across various populations and geographies, but real-world effectiveness was often limited by poor adherence[4-6].

Global and Indian Burden

- In 2023, 1.3 million new HIV infections occurred globally[1].
- In India, new infections were ~63,000, predominantly among high-risk groups[7].
- PrEP remains underutilized in India due to cost, lack of awareness, and implementation gaps.

Current PrEP Modalities

Table 1: Approved PrEP Agents

Regimen	Drug Class	Route	Dosing Frequency	Approval Year	Populations
TDF/FTC	NRTI	Oral	Daily	2012	All adults and adolescents
TAF/FTC	NRTI	Oral	Daily	2019	MSM and TGW only
Cabotegravir LA	INSTI	Intramuscular	Every 2 months	2021	All adults
Lenacapavir	**Capsid Inhibitor**	**SC**	**Every 6 months**	**2025**	**Women (cisgender)**

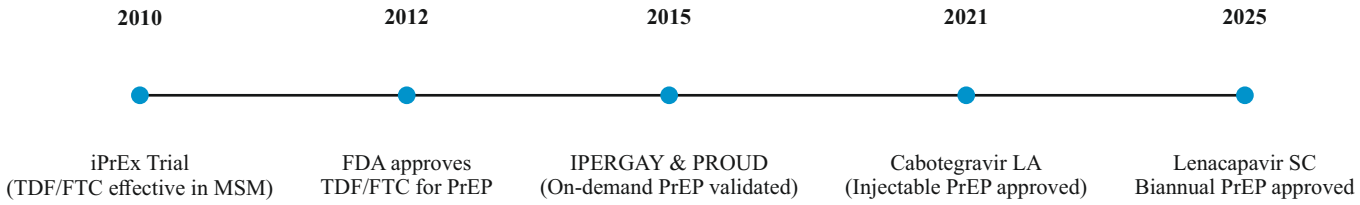

Figure 1: Timeline: Evolution of PrEP Strategies (Updated)

Lenacapavir: A Novel Long-Acting Agent

Mechanism of Action

Lenacapavir targets the HIV-1 capsid (p24), disrupting several essential viral processes:

- Uncoating of viral capsid
- Nuclear import of viral genome
- Integration into host DNA
- Virion assembly and maturation

This multi-step inhibition provides a strong resistance barrier and prevents cross-resistance with other ART classes[8].

Pharmacokinetics

- **Bioavailability**: High after SC administration
- **Half-life**: 12–16 weeks
- **Time to steady state**: 4–6 weeks
- **Metabolism**: CYP3A4 and UGT1A1
- **Therapeutic levels**: Maintained >6 months post-dose[9]

Clinical Efficacy: Key Trials

PURPOSE 1 Trial (2024)

- Phase 3 RCT in 5,300 cisgender women (South Africa & Uganda)[10]
- Arms: Lenacapavir SC q6 months vs daily oral TDF/FTC vs placebo

Findings

- **Lenacapavir**: 0 HIV infections
- **TDF / FTC**: 16 infections
- **Placebo**: 39 infections

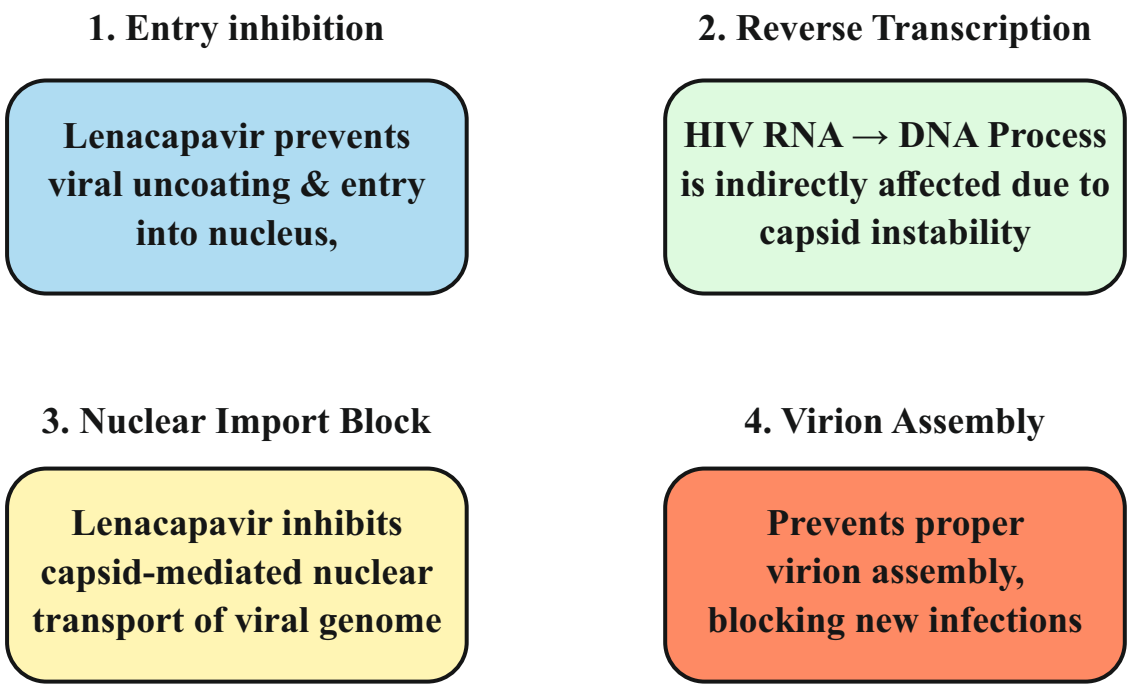

Figure 2: Mechanism of Action of Lenacapavir

Lenacapavir acts at multiple stages of the HIV lifecycle—including entry, reverse transcription, nuclear import, and assembly—by inhibiting the capsid protein (p24).

- Efficacy vs placebo: **100%**
- Mild injection site erythema in <5%

PURPOSE 2 Trial (Ongoing)

- Targeting MSM, TGW, non-binary individuals
- Interim data suggest >95% efficacy[11]
- Final results expected late 2025

Comparative Profile of PrEP Agents

Table 2: Comparative Features

Feature	TDF/FTC	Cabotegravir LA	Lenacapavir
Dosing	Daily	Every 2 months	Every 6 months
Route	Oral	Intramuscular	Subcutaneous
Mechanism	Reverse Transcriptase inhibitor	Integrase inhibitor	Capsid inhibitor
Adherence Needs	High	Moderate	Low
Resistance Risk	Present	Low	Minimal (PrEP use)
Cold Chain	No	Yes	No

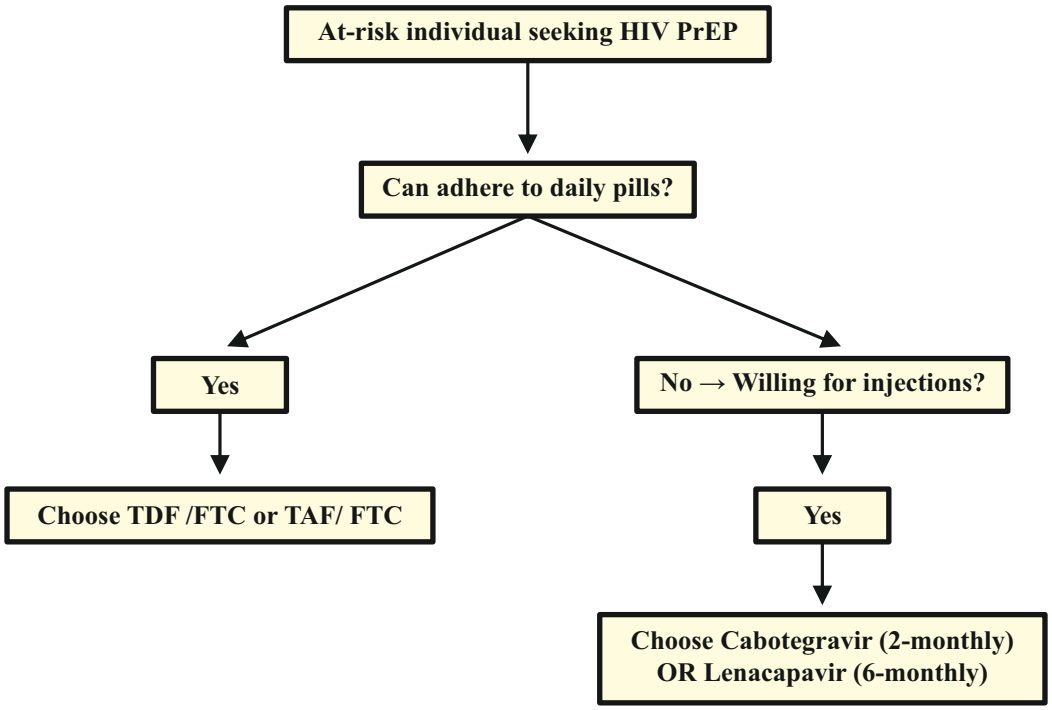

Figure 3: Flowchart: Choosing the Right PrEP Agent

Safety and Resistance Considerations

- **Resistance**: No significant mutations reported in PrEP use
- **Tolerability**:
    - No renal or hepatic toxicity
    - Mild injection site reactions
- **Drug Interactions**:
    - Avoid with strong CYP3A4 inducers (e.g., rifampicin)

Special Populations

Table 3: Lenacapavir in Special Populations

Group	Efficacy/Safety	Current Recommendation
Women (cisgender)	Proven in PURPOSE 1	FDA approved
MSM and TGW	Awaiting full results	PURPOSE 2 ongoing
Pregnant/Breastfeeding	Limited safety data	Not recommended
Adolescents	Trials ongoing	No approval yet
Renal Impairment	Safe	No adjustment required
Hepatitis Co-infection	No hepatotoxicity	Monitor LFTs if HBV/HCV co-infected

Implementation Challenges in India

Barriers

- No formal PrEP rollout in national HIV programs
- Lenacapavir is not yet approved in India
- High cost (INR 3–3.5 lakh per injection globally)

Opportunities

- Community-based PrEP via nurse-led models
- Integration with NACO and maternal-child health programs
- Long-acting profile is ideal for rural and mobile populations

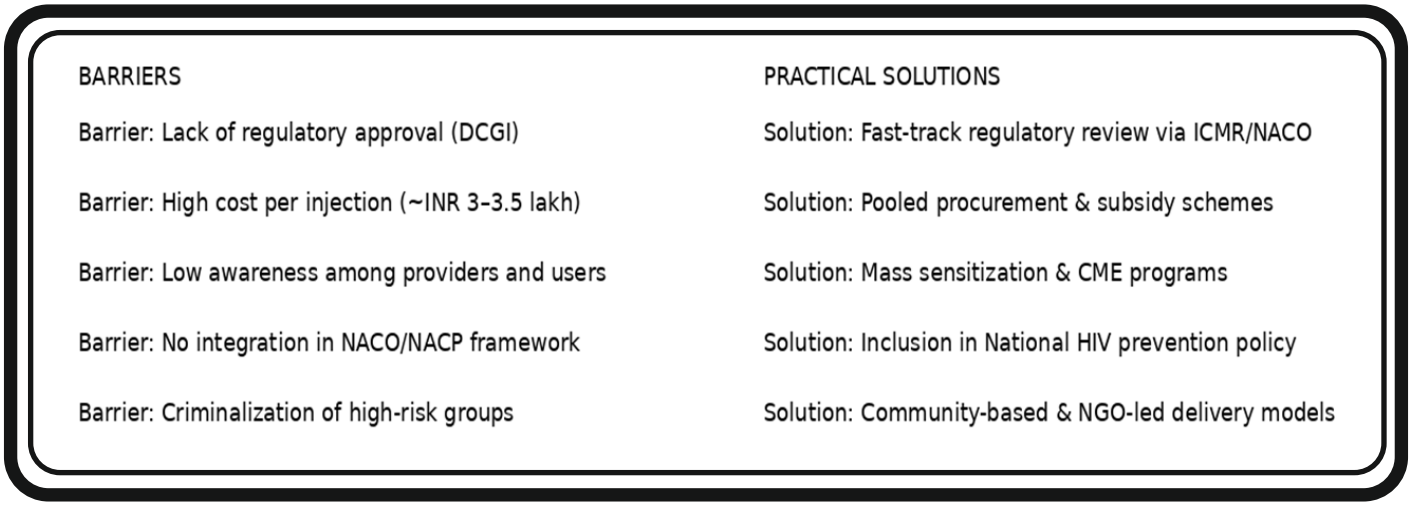

Figure 4: India-Specific Barriers and Solutions for Implementing Lenacapavir PrEP

Future Directions

- **Combination therapies**: Lenacapavir + islatravir trials underway
- **New delivery technologies**: Implants, microneedle patches
- **WHO prequalification**: Anticipated by late 2025
- **Public health modeling**: Assessing impact and cost-effectiveness in Low to middle Income Countries(LMICs)

CONCLUSION

Lenacapavir represents a milestone in the evolution of HIV prevention. With high efficacy, biannual dosing, and a novel mechanism of action, it addresses major limitations of daily oral PrEP. For India, the integration of Lenacapavir into prevention frameworks could offer a discrete, adherence-friendly option for high-risk individuals—provided challenges related to access, regulation, and cost are resolved.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Review

Stroke and Hyponatremia

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ABSTRACT

Stroke, or brain attack, occurs when blood flow to the brain is interrupted, either by a blockage or a rupture of blood vessel, causing brain cells to die from lack of oxygen and nutrients. The two main types are ischemic stroke and haemorrhagic stroke. The dyselectrolytemia particularly hyponatremia is significantly associated with adverse clinical outcomes, including higher stroke severity upon admission, prolonged hospital stays, and poorer functional outcomes at discharge. Importantly, hyponatremia has also been found to be a significant predictor of mortality. The prognostic accuracy of serum sodium levels in predicting mortality further emphasizes the clinical utility of monitoring electrolyte imbalances in stroke management. These results underscore the importance of early recognition and management of hyponatremia as part of comprehensive care strategies for acute ischemic stroke patients, aiming to improve out comes and enhance prognostic assessment in clinical practice.

KEYWORDS: Brain attack, Acute ischemic stroke, Hyponatremia

INTRODUCTION

Stroke is defined as "rapidly developing clinical evidence of focal (or global) impairment of brain function, with symptoms lasting 24 hours or longer, or leading to death with no evident cause other than vascular origin, "according to the World Health Organization (WHO)[1].

Stroke is subdivided into two types, ischemic stroke and haemorrhagic stroke. The majority of them, around 85%, are ischemic[2]. Ischemic stroke is caused by a thrombotic or embolic event that results in a reduction in blood supply to the brain. A thrombotic event occurs when blood flow to the brain is impeded within a blood vessel due to vascular malfunction, which is typically caused by atherosclerosis, arterial dissection, fibro muscular dysplasia, or an inflammatory illness. During an embolic event, material from other parts of the body obstructs blood flow through the afflicted channel[3].

Stroke is one of the leading causes of mortality and morbidity[4]. It is the world's second biggest cause of mortality. It affects 13.7 million people and kills 5.5 million people per year[5].

Stroke is the fourth leading cause of death and fifth leading cause of disability in India[6]. The crude annual incidence rate ranged from 108/100,000 to 172/100,000 people per year and the crude prevalence rate ranged from 26/100,000 to 757/100,000 people per year[7]. Stroke is a major cause of long-term disability among patients and has enormous emotional and socio-economic consequences.

Stroke assessment is required to predict and evaluate a patient clinical outcome. Different scoring systems and scales are used for stroke assessment. They assess the impact of therapeutic interventions in research and aids in improving diagnostic accuracy; helps determine clinical pathways of treatment, severity measurement and handoff Communication.

For Acute assessment of stroke scales used are Glasgow Coma Scale (GCS), NIH Stroke Scale (NIHSS), Modified NIHSS scale, and Intracerebral Haemorrhage Scale (ICH).

The National Institutes of Health Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items. For each item, a score of 0 typically indicates normal function, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. Maximum possible score is 42, with the minimum score being a 0[8].

The National Institutes of Health Stroke Scale (NIHSS) has emerged as a standard clinical tool for quantifying the neurological impairment caused by stroke.

The initial hours following an ischemic stroke are critical for both immediate survival and long-term functional outcomes. Recognizing the pivotal importance of this time frame, considerable efforts have been dedicated to identifying optimal diagnostic and prognostic tools and gaining a deeper understanding of the neurophysiologic alterations that occur during acute stroke. From a neurophysiologic standpoint, the occlusion of blood vessels leads to both localized changes, signifying the loss of function in the infarcted region, and widespread alterations in neural networks due to disruptions in structural and functional connectivity[9]. The activity changes within neural networks serve as an accurate reflection of the blood flow in the affected area. These dynamic alterations can provide insights into the improvement or deterioration of tissue perfusion. Swift restoration of blood flow in viable tissue is pivotal in halting the pathological cascade associated with ischemia, ultimately enhancing both local and global functional connectivity.

Hyponatremia, defined as a serum sodium level below135mEq/L, is a common electrolyte abnormality observed in patients with acute ischemic stroke. The presence of hyponatremia in the setting of acute ischemic stroke has been recognized as an important prognostic factor, with significant implications for patient outcomes[10].

The pathophysiology underlying the development of hyponatremia in acute ischemic stroke is multifactorial. The ischemic insult to the brain can lead to the release of various neuropeptides, such as antidiuretic hormone (ADH), which can stimulate water retention and cause dilutional hyponatremia. Additionally, the disruption of the hypothalamic-pituitary-adrenal axis and the release of inflammatory mediators can further contribute to the development of hyponatremia[11].

The mechanisms by which hyponatremia adversely affects the prognosis of acute ischemic stroke are not fully understood, but several proposed pathways have been suggested. Hyponatremia can lead to cerebral oedema, which can exacerbate the initial ischemic injury and contribute to further neurological deterioration. Additionally, hyponatremia has been associated with an increased risk of complications, such as seizures, respiratory distress, and electrolyte imbalances, all of which can negatively impact the clinical course and recovery of patients with acute ischemic stroke[12].

Moreover, hyponatremia may serve as a marker of the underlying severity of the ischemic insult and the patient's overall health status. Patients with comorbidities, such as heart failure, liver disease, or malignancies, are more prone to developing hyponatremia and may have a poorer prognosis due to their overall frailty and the increased vulnerability of the brain to ischemic injury.

It is important to note that the severity and duration of hyponatremia may also play a role in the prognosis of acute ischemic stroke. Severe and persistent hyponatremia, which is more challenging to correct, may be associated with a worse prognosis compared to mild or transient hyponatremia.

In clinical practice, the early recognition and management of hyponatremia in patients with acute ischemic stroke are crucial. Prompt identification and appropriate correction of the electrolyte imbalance, while considering the potential risks of rapid sodium correction, may help improve patient outcomes. Additionally, the integration of hyponatremia as a prognostic factor in risk assessment models for acute ischemic stroke may aid clinicians in stratifying patients and guiding their management strategies[12].

The presence of hyponatremia in patients with acute ischemic

stroke is an important prognostic factor, associated with a higher risk of mortality and poor functional outcomes. Understanding the pathophysiological mechanisms and the clinical implications of hyponatremia in this setting can inform the development of targeted interventions and improve the overall management of patients with acute ischemic stroke.

REVIEW OF LITERATURE

Stroke, a neurological disorder characterized by blood vessel blockage, is often associated with the development of clots within the brain, disrupting normal blood flow and leading to arterial blockages that can cause vessel rupture and subsequent bleeding. The abrupt cessation of oxygen supply to the brain cells due to the bursting of arteries can result in the sudden death of these cells. Common repercussions of stroke include the onset of dementia and feelings of despair. Notably, stroke was traditionally classified as a blood vessel disease until the revision of the International Classification of Diseases 11 (ICD-11) in 2018.

Stroke Risk Factors:

- Gender: The risk of stroke is elevated in men, with a 1.3 times higher risk compared to women, except at the highest ages where the difference diminishes. Women, however, have a larger risk of subarachnoid haemorrhage.
- Age: Stroke incidence increases with age, with a more than doubled risk after 55 years of age, and the risk rising with each subsequent decade.
- Ethnicity: Individuals of African descent face a higher stroke risk than Caucasians, attributed to the inadequate management of curable risk factors. Chinese individuals have a higher rate of intracerebral bleeding, while East Asians and African Americans exhibit a higher rate of intracranial artery stenosis in ischemic stroke[13].
- Genetic: Various genetic conditions, including CADASIL, CARASIL, MELAS, homocystinuria, and Fabry disease, manifest with stroke or stroke-like episodes. Sickle cell anaemia in children increases the risk, and specific genetic markers are associated with ischemic stroke and lobar intracerebral haemorrhage[14-18].
- Diabetes Mellitus (DM): Diabetes causes arterial deterioration, increasing the risk of ischemic stroke. Recurrent strokes are more common in individuals with diabetes[19].
- Hypertension: Both systolic and diastolic blood pressure contributes to stroke risk, with a significant increase in the chance of stroke death associated with elevated blood pressure.
- Stroke or Transient Ischemic Attack (TIA) in the Past: Previous stroke or TIA significantly raises the risk of subsequent strokes, particularly in individuals with diabetes, those over 60 years old, and those with prolonged or TIA with weakness or speech disturbance.
- White Matter Disease: Both periventricular and subcortical white matter hyperintensities independently increase the risk of subsequent stroke.
- Dyslipidaemia: Increased cholesterol levels contribute to atherosclerosis, raising the risk of cerebral infarctions, while low cholesterol increases the risk of intracerebral haemorrhage[20,21].
- Disorders of Coagulation: Ischemic stroke is linked to coagulation disorders, including antiphospholipid antibodies and lupus anticoagulants.
- Obstructive Sleep Apnoea (OSA): OSA, a risk factor for stroke, may raise blood pressure, lead to obesity, and contribute to hypercoagulability, atherosclerosis, and reduced cerebral blood flow.
- Renal Disease: Renal disease heightens the risk of stroke in individuals with atherothrombotic disease, and microalbuminuria is independently linked to stroke.
- Cardiac Factors: Atrial fibrillation, cardiomyopathies, patent foramen ovale (PFO), and valvular heart disease increase the risk of stroke.
-

Lifestyle Factors:

- Smoking: Increases the risk of both ischemic and haemorrhagic strokes.
- Alcohol: Excessive alcohol consumption raises stroke risk, while moderate alcohol intake may result in a modest increase.
- Diet: Fruits, vegetables, and fish consumption can help prevent strokes.
- Physical Activity: Regular exercise reduces stroke risk.

- Obesity: Elevated BMI increases the risk of ischemic stroke.
- Hormonal Therapy/ OCP: Hormone-based therapies are associated with an increased risk of stroke.
- Stress: Self-perceived psychological stress increases stroke risk.

Socioeconomic Factors: Lower socioeconomic status is linked to a higher stroke risk[22,23].

Understanding these diverse risk factors is crucial for implementing preventive measures and tailored interventions to mitigate the risk of stroke in different populations.

Pathogenesis:

The brain typically receives 55 to 70 millilitres of blood per 100 grams of brain tissue per minute, ensuring its normal functioning. Prolonged ischaemia with hypoxia can lead to neuronal and glial cell death when blood flow falls below15mL/100g/min[24]. Various factors, including mean arterial blood pressure, cerebral vascular resistance, local metabolic products (such as pH, PaO2, PaCO2), and other known and unknown processes, contribute to maintaining blood flow. Autoregulation modulates regional blood flow to meet the specific metabolic demands of different brain regions[25-28].

The brain exhibits auto regulation to adjust blood flow based on local metabolic needs, with variations in blood flow across different brain areas. However, in regions affected by cerebral ischaemia, self-regulation is diminished, and the microvasculature becomes less responsive to pressure changes, vasoactive drugs, and other stimuli. Cerebral oedema may develop in the presence of vascular leakage.

To protect the brain from ischaemia, several collateral routes exist. Major extracranial arteries, including carotid and vertebral arteries, form well-calibrated, low-resistance anastomosis at the base of the brain. Additionally, post-Willis anastomosis help mitigate the effects of blockage in single cortical branches. Nevertheless, in conditions like generalized arterial disease, multiple bypassed stenotic lesions (as seen in atherosclerosis), or with aberrant/ congenital abnormalities, these collateral routes may prove insufficient, increasing the susceptibility to cerebral ischaemia and subsequent brain infarction[28-29].

Circle of Willis:

Cerebral arterial circle is formed at the base of the brain by the interconnecting vertebrobasilar and internal carotid arteries. These interconnections achieved by an anterior communicating artery which interconnects left and right anterior cerebral arteries, 2 posterior communicating arteries one on each side connects posterior cerebral artery with the internal carotid artery [Figure 1].

Clinical Features:

During a general physical examination, identifying obesity, weak or absent peripheral artery pulsations, vascular bruits, uneven or increased blood pressure, postural hypotension, and retinopathy is crucial. Approximately 60% of patients may experience prodromal warning symptoms of Transient Ischemic Attack (TIA). TIA episodes are typically brief, lasting from a few minutes to less than an hour, occurring alone or in succession over hours, days, or months, and usually leaving no lasting effects. Unlike TIAs, which are not usually linked to posture or blood pressure and can resolve completely, 10%to 15% of patients may experience a developing or full-blown stroke after the last ischemic period. In cases of a stroke occurring in stages ('thrombosis in evolution'), symptoms may appear in each leg sequentially or simultaneously. Atherothrombosis is characterized by stuttering or intermittent progression.

Occasionally, a stroke may present as a single large catastrophic occurrence (accomplished infarction or completed stroke). The clinical symptoms vary depending on the location of arterial blockage[29].

Internal Carotid Artery Syndrome:

In proximity of the carotid sinus, the cervical segment of the internal carotid artery is a prevalent site for atherostenosis, where approximately 60% of thrombotic lesions manifest. Due to collateral anastomoses, these tumours often remain asymptomatic, facilitated by external carotid-ophthalmic anastomoses, superficial and deep cervical anastomoses, or connections with the opposite carotid artery through the anterior segment of the Circle of Willis. In nearly 50% of cases, warning symptoms precede a significant ictus, marked by transient perplexity and difficulties in speech (aphasia, dysarthria, dyslexia), sensory paraesthesia with or without muscular weakness on the opposite side. Amaurosis fugax, characterized by transient monocular blindness, is pathognomonic for carotid artery syndrome, albeit affecting only 15% to 20% of individuals[30].

Acute blockage of the carotid artery exhibits clinical symptoms nearly identical to those of middle cerebral syndrome. Physical

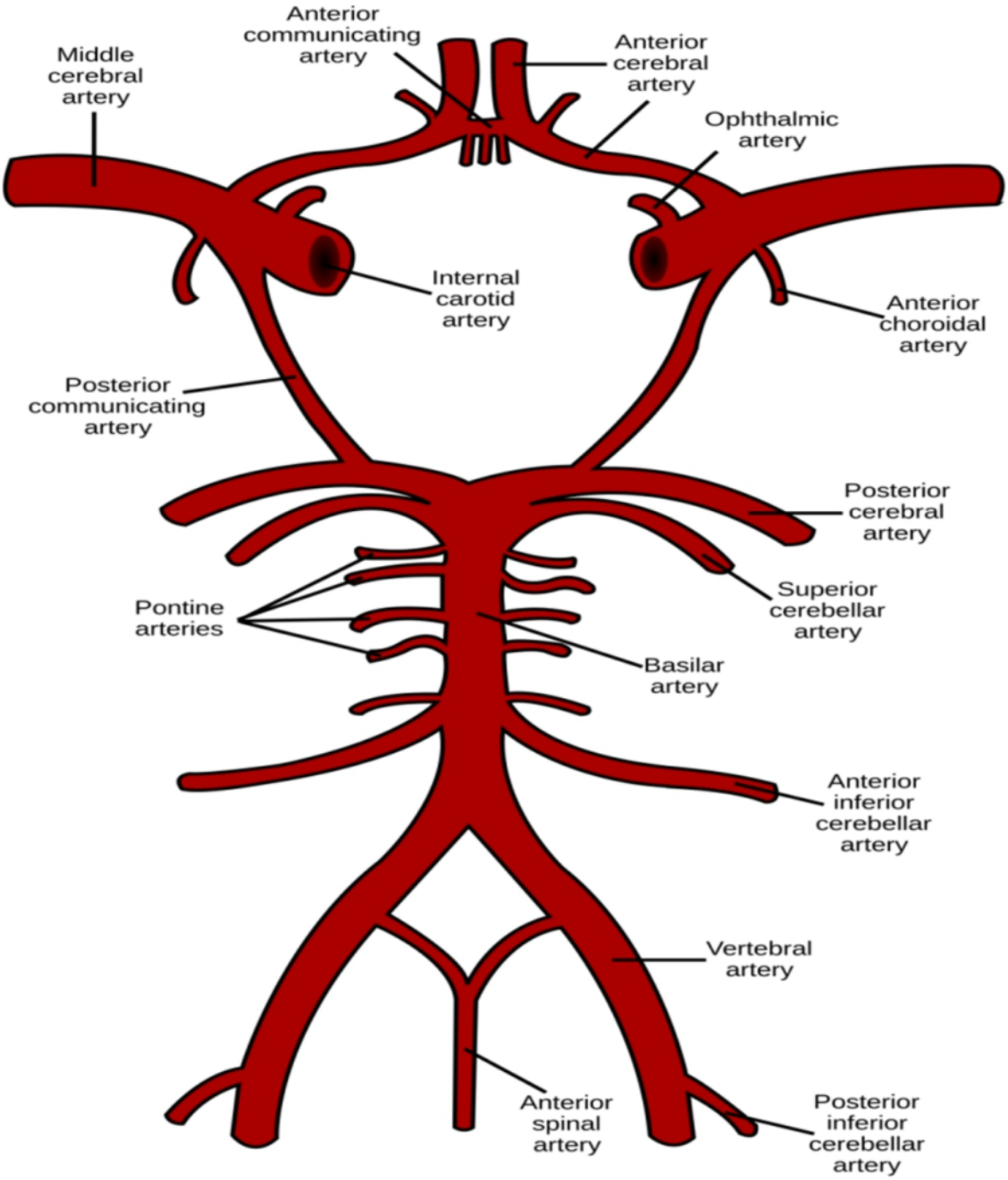

Figure 1: Circle of Willis

indicators on the side of the suspected lesion, such as weak internal carotid or superficial temporal artery pulsations, dilated pupil, poorly pulsing retinal vessels, and ocular or cervical bruits on the ipsilateral side, aid in accurate diagnosis. Carotid duplex Doppler sonography and angiography are crucial for determining the extent and degree of stenosis. Notably, a fresh occlusive carotid artery lesion on the opposite side of a patient with an old or silent occlusive carotid artery lesion on one side can be fatal. The clinical scenario of bilateral hemiplegia (quadriplegia) with coma may be misconstrued as basilar artery syndrome, emphasizing the need for precise differentiation[30].

Asymptomatic Cervical Bruit:

Approximately 5% of asymptomatic elderly individuals (aged 55 to 80 years) may exhibit a carotid bruit in the neck. However, establishing a direct link between the mere presence of a bruit and subsequent Transient Ischemic Attack (TIA) or stroke in that territory is challenging unless the bruit is haemodynamically significant. Clinical trials have not conclusively demonstrated the efficacy of preventive endarterectomy. Averting future strokes, estimated at 6% within the next three years. Antiplatelet therapy may be considered in such instances[30].

Middle Cerebral Artery Syndrome:

Cortical branches supplying the lateral surface of the cerebral hemisphere present varying symptoms upon blockage of the middle cerebral artery. Common manifestations encompass contralateral hemiplegia, hemianaesthesia with or without homonymous hemianopia, and aphasia (dominant hemisphere). Occlusion of the superior division results in contralateral hemiparesis, sensory deficits, and expressive aphasia (Broca's aphasia), while inferior division lesions on the dominant side lead to Wernicke's aphasia (sensory aphasia). Monoplegic symptoms due to a single cortical branch injury are not uncommon. A sensorimotor hemiplegic syndrome ('capsular- hemiplegia') attributed to occlusion of penetrating branches (lenticulostriate arteries) may lack severe sensory loss, and 'pure motor hemiplegia' is typical[31].

Anterior Choroidal Artery Syndrome:

The anterior choroidal artery plays a crucial role in providing corticospinal and sensory fibers for the contralateral limb to the posterior limb of the internal capsule. This distinctive syndrome, known as 'capsular-hemiplegia,' is characterized by dense hemiplegia, hemianaesthesia, and homonymous hemianopia.

Anterior Cerebral Artery Syndrome:

The cortical branches predominantly supply the medial superior surface of the frontal lobe and the parietal lobe up to the paracentral lobule. In cases of asymmetrical Circle of Willis, blockage of the anterior cerebral artery proximal to the anterior communicating artery often remains asymptomatic. However, occlusion distal to the anterior communicating artery manifests as sensorimotor paralysis of the opposite lower extremity, slight weakening of the opposite shoulder, and may be accompanied by mental alterations, ictal and urine incontinence, gait problems, apraxia, grab and sucking reflexes. Occlusion of an unpaired anterior cerebral artery, supplying both hemispheres, leads to a cortical form of paraplegia with sphincter incontinence and a mental state where the patient is alert but mute (akinetic mutism). Notably, hemianopia and aphasia are not observed. Ataxic tremors of the contralateral limbs are often attributed to occlusion of penetrating branches and Heubner's artery (frontal ataxia), and various possibilities include apraxia, ideomotor dyspraxia of the limbs, and abnormal gait.

Posterior Cerebral Artery Syndrome:

The medial and inferior aspects of the occipital and temporal lobes receive blood supply from the posterior cerebral artery. Its branches also serve the midbrain, cerebral peduncle, thalamic, and subthalamic areas. Embolic blockage of the posterior cerebral arteries may occur, presenting with a major feature of contralateral homonymous hemianopia resulting from infarction of the primary visual area (calcarine cortex). Central vision is usually spared, even in cases of bilateral illness, a phenomenon termed 'gun-barrel vision'. Visual dysfunction includes illusory or distorted vision, visual- object agnosia, and various forms of dyslexia without dysgraphia. Pupillary reflexes are generally intact. Other potential manifestations encompass contralateral hemiplegia (peduncular hemiplegia) and thalamic syndrome (Dejerine-Roussy syndrome) due to a lesion in the cerebral peduncle. The thalamic syndrome may exhibit a varied degree of sensory loss in all modalities, and spontaneous scorching or agonizing symptoms are common (analgia dolorosa). Memory loss (amnesia) indicates medial temporal brain damage, while ataxic tremors or contralateral involuntary choreoathetosis are infrequent[31].

Vertebrobasilar Syndrome:

The vertebral arteries converge intra cranially, forming the basilar trunk after traversing the bony vertebral canals. The entire brainstem, cerebellum, and vestibular apparatus receive

their blood supply from the short paramedian and long circumferential branches of these arteries. Symptoms of Transient Ischemic Attack (TIA) encompass vertigo, dizziness, diplopia, dysarthria, dysphasia, incoordination of gait and limbs, and bilateral evidence of sensorimotor impairment. Occipital headaches may also be present. Specific localizations can aid in diagnosis: ipsilateral3rdnerve palsy with contra lateral hemiplegia indicates midbrain localization (Weber's syndrome), while crossing cerebellar ataxia signifies pontine involvement (Claude's syndrome). Homolateral paralysis of the 7th nerve with contralateral hemiplegia and hemianaesthesia points to a pontine lesion (Millard-Gubler syndrome). Palatal paralysis and limb ataxia, along with impaired posterior column sensibility on the same side and reduced pain and temperature perception on the opposite limbs, suggest lateral medullary infarction (Wallenberg's syndrome). Infarction of the basis point is due to mid-basilar occlusion can result in quadriplegia with bilateral conjugate lateral gaze palsy and a 'mute state' while retaining full consciousness ('locked-in syndrome'). Additionally, occlusion of single cerebellar branches may cause dizziness, nausea, vomiting, nystagmus, and appendicular or truncal ataxia without sensorimotor loss, requiring differentiation from cerebellar bleeding that may necessitate urgent surgical decompression.

Aortic Arch Syndrome:

This enigmatic clinical condition is characterized by decreased or absent arterial pulsations in the arms and neck, with roots of the disease, regardless of etiology, near the origins of large vessels emerging from the aortic arch. Potential causes include congenital anomalies, trauma with or without aneurysm, chronic dissecting aneurysm, mediastinal tumours, thrombophilia, syphilitic aortitis, and atheromatosis. It is noteworthy that an arteritis of unknown origin may be responsible for a significant number of female cases. Although many cases of aortic arch syndrome reported from India are often presumed to be rheumatic, syphilitic, or unexplained arteritis, it is now recognized that the primary lesion, especially in men, may not always be arteritis[31].

Assessment of Acute Stroke Syndrome:

Primary Evaluation: Initiate the assessment by prioritizing the ABCs (airway, breathing, and circulation), as patients with stroke may exhibit reduced levels of consciousness, necessitating potential intubation. Additionally, circulatory instability linked to arrhythmia or concurrent cardiac conditions is an infrequent yet critical consideration[32].

Quick Disability Assessment:

- Speech and Spatial Perception: Identify aphasia or hemispatial neglect
- Vision: Determine the presence of hemianopia or quadrantanopia
- Hemiparesis: Assess facial droop, antigravity arm strength, and antigravity legs` strength
- Hemianesthesia: Check gross light touch on the face, arm, and leg
- Coordination and Walking: If feasible, have the patient ambulate to assess coordination and walking ability

Utilize NIH Stroke Scale:

Employ the National Institutes of Health Stroke Scale (NIHSS) to guide disability assessment[33]:

- NIHSS=0–5: Transient ischemic attack or minor stroke
- NIHSS=6–10: Moderate disabling stroke
- NIHSS= 11–20: Moderate to severe disabling stroke
- NIHSS≥20: Severe, life-threatening stroke

Confirmatory Diagnosis:

Brain and neurovascular imaging are imperative for diagnosis. Non-contrast computed tomography (CT) of the head is the current standard, offering speed and widespread availability. Expert interpretation of head CT can accurately diagnose haemorrhagic stroke (intra-cerebral or subarachnoid haemorrhage) in over 95% of cases. While CT is highly sensitive to major ischemic strokes, its capability to detect minor strokes is limited due to resolution constraints. Magnetic resonance imaging (MRI) is preferred for minor strokes with mild deficits, providing higher spatial resolution for conclusive imaging diagnosis[34].

Imaging Recommendations:

- Non-contrast Head CT:
    - Rules in haemorrhagic strokes with high accuracy
    - Highly sensitive for major ischemic strokes
    - Limited sensitivity for minor strokes[35]
- CT Angiography (Following Head CT):
    - Essential for identifying occluded intracranial vessels

- Evaluates extra cranial carotid, vertebral, aortic arch, and proximal great vessels
- Critical for management of transient ischemic attack, minor stroke, and major ischemic stroke[35,36]

- MRI:
  - Greater sensitivity for small-volume ischemia
  - Utilized in non-urgent situations for follow-up imaging
- Haemorrhagic Stroke Imaging:
  - In cases of haemorrhagic stroke, intracranial CT angiography identifies intracranial aneurysms or bleeding sources[36]

Unlike acute coronary syndromes, there are no available bloods or electrophysiology tests for stroke diagnosis; imaging serves as the primary diagnostic biomarker.

Neurophysiologic Tools in the Evaluation of Ischemic Stroke:

The exploration of cerebral perfusion in humans' dates back to the 1950s, with early studies indicating that neurological impairment occurs when cerebral blood flow (CBF) drops below 29mL/100g/min[37]. Subsequent research by Jennet et al. revealed that hemiparesis consistently manifests when relative cortical CBF falls below 30% compared to baseline levels[38]. Animal studies later identified a critical threshold of 18mL/100g/min for irreversible brain tissue damage after vessel occlusion[39]. However, various individual factors, including age, brain structural reserve, and collateral circulation, contribute to tissue vulnerability post-occlusion. Adequate collateral blood flow is crucial, limiting the infarct core size and favouring the ischemic penumbra—hypoperfused and hypoxic brain tissue surrounding the core, potentially salvageable with reperfusion. Advances in acute stroke management, extending the reperfusion time window, emphasizes electing patients with a large ischemic penumbra and a small infarct core using perfusion imaging[40].

Perfusion imaging, despite offering a "snapshot" of cerebral blood flow, lacks the capacity to capture stroke evolution. MRI and CT scans provide short-term prognostic parameters, reflecting the risk of infarction in the absence of reperfusion and the degree of collateral circulation[41]. Stroke's pathological process extends beyond the acute phase, initiating a long-term cascade of events, including changes in cortical excitability, often preceding clinical evolution. Conventional neuroimaging struggles to detect these changes, while electrophysiological techniques, such as Electroencephalogram (EEG) and transcranial magnetic stimulation (TMS), offer the advantage of capturing the dynamic nature of stroke.

EEG records synchronized synaptic activity in cortical neuron populations. Animal studies indicate that EEG reflects cerebrovascular reactivity in the penumbra after vessel occlusion, while TMS captures cortical circuit reorganization and changes in functional connectivity due to plasticity mechanisms in later stages. Therefore, electrophysiological techniques serve as complementary tools to neuroimaging for functional and structural evaluations of the brain post-stroke.

The Pathological Evolution of Brain Infarction:

Insufficient blood flow to the brain, unable to meet metabolic demands, results in cerebral ischemia. This insufficiency can be focal, as observed in the obstruction of a vessel supplying blood to the brain, or global, as in the case of cardiac arrest. In stroke situations, the diminished supply of oxygen and glucose to energy-demanding brain cells—primarily neurons but also glial cells—initiates a time-dependent cascade of effects.

The ischemic cascade provides a simplified overview of the primary pathological mechanisms occurring during acute ischemic stroke [Figure 2].

Neurophysiologic Aspects of Ischemic Stroke Progression:

From a neurophysiologic perspective, the ischemic region is characterized by electrical silence. There lease of calcium and excitatory neurotransmitters leads to peri-infarct depolarization (PID), propagating across the surrounding area. PID is not just an epiphenomenon but induces calcium accumulation, contributing to delayed secondary pathology and neuronal death. Neurons in the penumbra, functionally impaired and electrically silent due to membrane potential imbalance, remain anatomically preserved. Prolonged blood flow restriction in the penumbra leads to damage through inflammation, apoptosis, oxygen-reactive species, ionic imbalance, protease activation, and DNA disruption[42].

In the acute phase, compensatory collateral recruitment occurs through arterial collateral remodelling, mitigating damage caused by sudden distal pressure drop due to vessel occlusion. Excitotoxicity and oxidative stress decrease in the subacute stage, giving way to increased glial activation and neuroinflammation. Approximately two weeks after the stroke, an immature glial scar begins to form, progressing to a mature

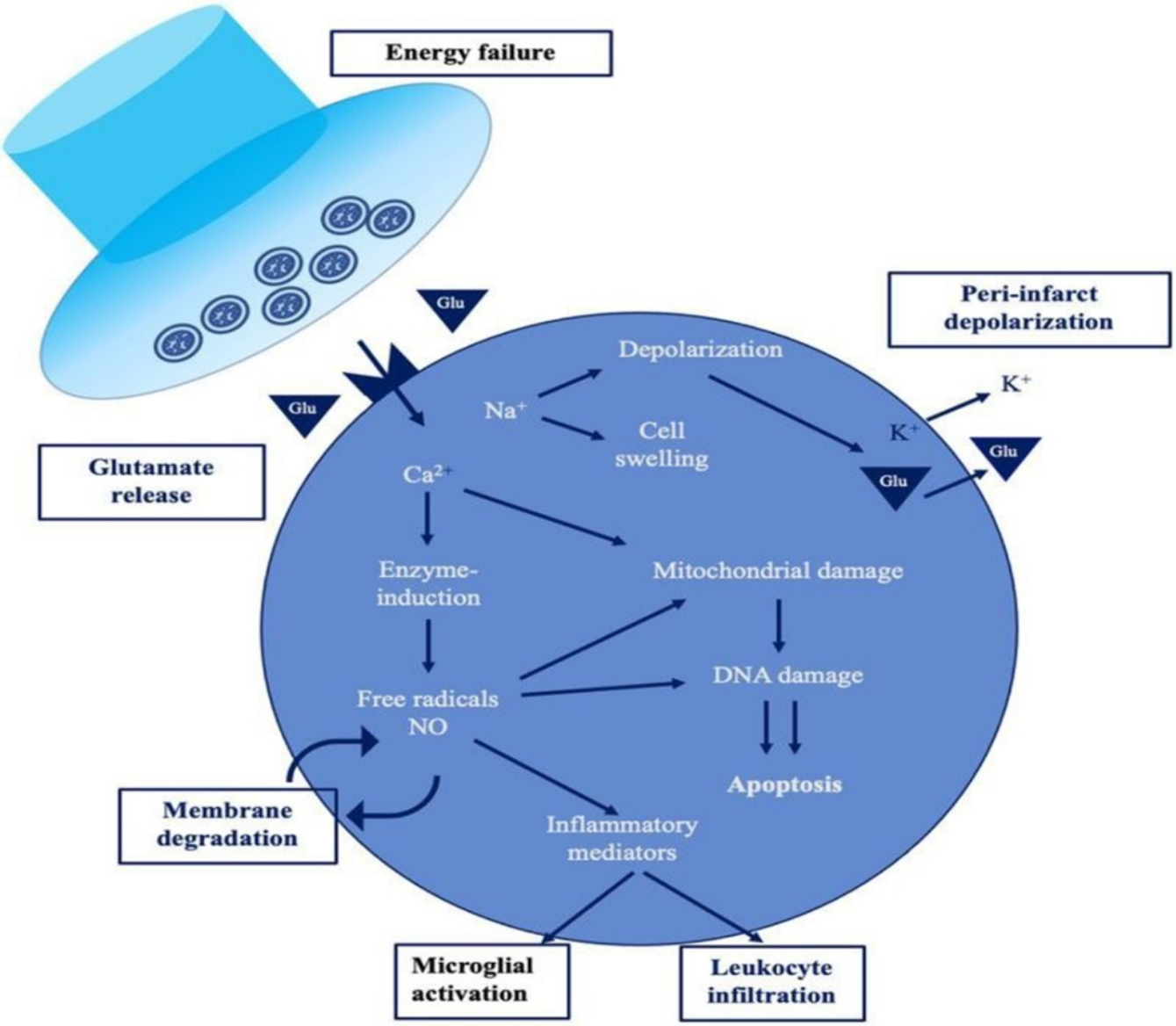

Figure 2: The Ischemic Cascade

glial scar around seven weeks, defining the chronic phase[43].

For the purposes of this review, **stroke "time points"** are categorized as "acute" within the first 7 days, "subacute" within 6 months, and "chronic" after 6 months[44]. However, the lack of a standardized definition for stroke "time points" in the literature poses a major limitation.

The reduction of cerebral blood flow significantly impacts brain oscillations as maintaining ionic gradients and membrane potential consumes substantial energy. Neurons, with varying vulnerability to hypoxia, experience decreased signal power of high-frequency waves early in stroke. Prolonged blood flow interruption leads to synaptic dysfunction, neural function suppression, and eventual cell death. Oxygen and glucose deprivation induce membrane ATPase failure, causing intracellular Na and Ca^{2+}influx, neuronal depolarization, and excitotoxicity. Hypoxia damages the blood- brain barrier, promoting early inflammation through neutrophil and lymphocyte migration[45].

Monitoring Stroke Evolution through Neurophysiologic Tools:

Neural oscillations serve as crucial communication channels among neurons in the brain, observable as large-scale oscillations in the EEG signal at the cortical level.

Additionally, tools like functional magnetic resonance imaging (fMRI) and non-invasive brain stimulation (NIBS), such as transcranial magnetic stimulation (TMS), have been employed for in-vivo studies of human networks[46].

EEG, a non-invasive tool, has been extensively utilized for stroke diagnosis and prognosis. It reflects extracellular currents resulting from excitatory and inhibitory postsynaptic currents of cortical pyramidal cells. Quantitative EEG (qEEG) measures, including frequency spectrum analysis and topographic mapping, offer a standardized approach for outcome prediction in ischemic stroke. Parameters derived from the EEG power spectrum, such as the delta/alpha power ratio, have demonstrated significant correlations with clinical status, enabling a more accurate categorization of stroke severity and serving as reliable prognostic indicators[47].

NIBS techniques, assessing functional alterations in cortical excitability and plasticity propensity post-stroke, can also evaluate connectivity. TMS, a non-invasive and painless technique, applied over the primary motor cortex (M1), induces a descending volley in the corticospinal pathway, eliciting a motor evoked potential (MEP) in contralateral limb muscles. Over the past 30 years, TMS has been instrumental in studying the pathophysiology of various disorders, optimizing single-pulse, paired- pulse, and repetitive stimulation protocols. In the acute phase after stroke, TMS provides insights into changes in neural circuits, cortical excitability, reorganization phenomena, and functional recovery prediction[48-50].

Recent advancements in TMS technology have introduced TMS-EEG, enabling the direct recording of magnetic stimulation output at the scalp. TMS-EEG, by eliciting TMS evoked potentials (TEPs) characterized by positive and negative waveforms, serves as an indirect measure of the functional integrity of cortical structures. Stroke patients benefit from TMS-EEG applications, providing valuable information about cortical structural integrity and brain connectivity[51].

Neurophysiological Dynamics in the Acute Phase of Ischemic Stroke:

The initial hours following an ischemic stroke play a pivotal role in both immediate survival and long-term functional outcomes. Due to the critical nature of this phase, considerable efforts have been directed towards identifying optimal diagnostic and prognostic tools and comprehending the neurophysiological changes that unfold during acute stroke. From a neurophysiological standpoint, vessel occlusion triggers both local alterations, reflecting the loss of function in the infracted area, and widespread changes in neural networks, disrupting structural and functional connectivity[52]. These network activity changes accurately mirror blood flow conditions in the affected region, offering dynamic insights that signify either improvement or deterioration in brain tissue perfusion. Rapid restoration of blood flow in viable tissue halts the ischemic pathological cascade, leading to enhanced local and global functional connectivity[53,54].

EEG Studies: In the immediate aftermath of vessel occlusion, there is an emergence of high-amplitude slow activity, particularly in the delta frequency band (1–3 Hz), within the affected brain regions[55-57].

In the intermediate stage of ischemia, specifically in penumbra tissue, EEG alterations may be less pronounced, involving the attenuation of beta activity and alpha slowing[59]. In an animal model of ischemia, a notable surge in alpha band power during vessel occlusion, succeeded by a marked increase in delta power, has been reported. Delta activity, indicative of cerebral dysfunction, is consistently correlated with lesion location on neuroimaging, particularly evident on fronto-temporo-central electrodes post-middle cerebral artery stroke[60].

Vascular insults induce a frequency activity imbalance between hemispheres, characterized by reduced higher frequency activity and increased low-frequency bands on the affected side. The Brain Asymmetry Index (BSI), a motor functioning and recovery biomarker post-stroke, demonstrates higher values in acute stroke patients, tending to normalize with spontaneous recovery. Favourable motor recovery is often predicted by the reestablishment of balanced high-frequency activity between motor areas, although the role of the contralesional hemisphere remains a topic of debate and might be contingent upon stroke type and deficits[61].

Greater delta and theta activity within 24 hours from onset, coupled with decreased faster activity and increased inter hemispheric asymmetry, are linked to poor outcomes on the modified Rankin Scale (mRS) at discharge and a worsened prognosis[62]. Recent studies correlating changes in quantitative EEG (qEEG) measures with long- term prognosis in acute stroke patients undergoing mechanical thrombectomy reveal

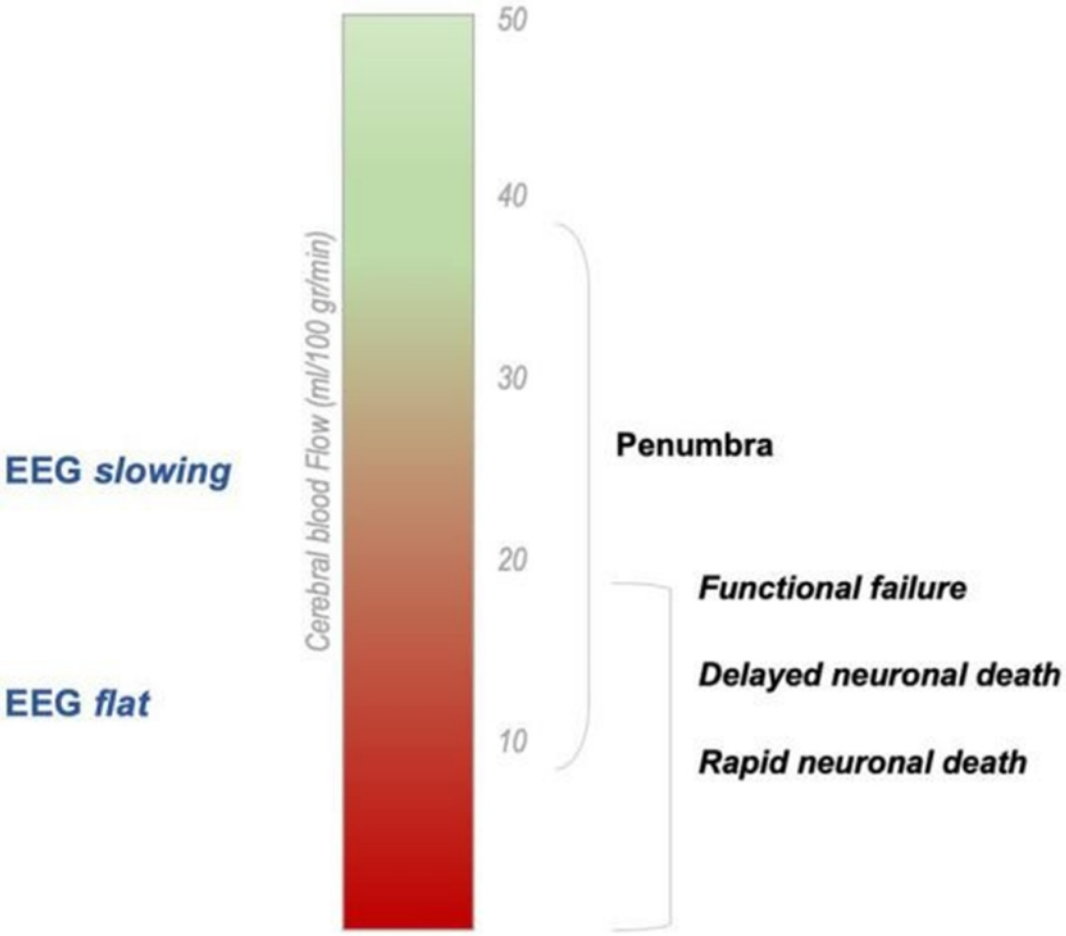

Figure 3: Cerebral blood Flow related to Electroencephalographic findings in acute stroke. In acute ischemic stroke, EEG signals undergo changes commensurate with reductions in cerebral blood flow (CBF). The infarcted area, where damage is irreversible, typically exhibits electrical silence on EEG.

that delta power 24 hours post-procedure and the interhemispheric delta-alpha ratio serve as robust prognostic markers, outperforming CT perfusion values[63].

Power measures, especially delta activity, exhibit associations with regional cerebral blood flow (CBF), showing a negative correlation with delta and a positive correlation with alpha. These measures dynamically change in reflection of blood flow status; after reperfusion, there is a sudden increase in theta, alpha, and beta wave band power, accompanied by a significant drop-in delta activity that may persist for a duration. Continuous EEG monitoring during thrombolysis and thrombectomy has been proposed due to these dynamic changes, with a reduction in delta activity noted within 20 minutes after r-tPA administration[63].

qEEG measures include more intricate indices such as delta/theta ratio (DTR), delta/alpha ratio (DAR), and (delta+theta)/(alpha+beta) ratio (DTABR). In an animal model of middle cerebral artery occlusion, transiently increased periodic spectral exponents in the peri-infarct are correlated with better recovery. Indices assessing the 1/f shape of the EEG spectrum have been proposed for a comprehensive assessment of the excitation/inhibition balance expressed in EEG. These parameters show promise in monitoring stroke evolution, accurately reflecting changes in blood flow status[64].

Higher values of DTR, DAR, and DTABR observed during ischemia rapidly decrease after reperfusion. Continuous EEG during thrombectomy revealed a significant reduction in DAR within minutes of middle cerebral artery reperfusion, preceding clinical symptom improvement. This suggests that DAR serves as an immediate index for salvaging the penumbra and aiding clinicians in predicting clinical outcomes in conjunction with imaging evidence of reperfusion[64].

In animal models of hypoxic brain conditions, a rapid reduction in EEG signal amplitude has been observed as one of the earliest features following vessel occlusion, persisting even after reperfusion, potentially acting as a "safety mechanism" to reduce neuronal metabolism and protect cells. Nevertheless, reduced electro cortical brain activity after blood flow restoration is associated with lower oxygen utilization, implying potential long-term brain damage. In this context, neuroprotective treatments may be beneficial in shielding tissue from delayed injury mechanisms and preserving plasticity propensity during this stage[62].

Neurophysiological Changes During the Sub acute Phase of Stroke:

In the subacute phase of stroke, the ischemic lesion undergoes better definition, and variable hypoperfusion may persist in the surrounding brain tissue. During both the acute and subacute phases of stroke, neuroradiological findings may not directly correlate with clinical impairment due to dynamic changes in the hypoperfused area and the extent of surrounding oedema. Overtime, additional factors like neuroplasticity and the brain's structural reserve may influence clinical presentation. Given that neurons are organized in networks, clinical manifestations are not solely dependent on the loss of function in the lesioned area but also on the global impairment of medium and large-scale circuits. Focal brain lesions can functionally impair remote regions, a phenomenon known as "diaschisis," wherein the excitability and metabolism of remote regions, including the hemisphere contra lateral to the stroke side, are reduced[65]. Neuro-inflammatory mechanisms and vasogenic oedema due to tight junction disruption may further influence lesion consolidation and neurological impairment.

Quantifying EEG and TMS changes during this stage is crucial for defining the extent of brain damage post-stroke.

EEG Studies:

EEG and quantitative EEG (qEEG) measures serve as valuable prognostic tools in the subacute stage. Slower frequencies may persist on electrodes overlying the lesioned area even after the acute stage, with the magnitude of this activity dependent on infarct volume[61]. In a study on the subacute stage, whole EEG power remained lower than that of the control group even after reperfusion, and indices such as delta/theta ratio (DTR), delta/alpha ratio (DAR), and (delta + theta)/ (alpha + beta) ratio (DTABR) remained relatively high. This likely indicates the persistence of ischemic stunning in the brain and disruption of neural networks in later stages of stroke[66].

In subacute middle cerebral artery stroke, the reduction of asymmetry in high-frequency activity between affected and unaffected hemispheres correlated with better motor performance over time. A higher Brain Asymmetry Index (BSI) value in the subacute phase strongly indicates poor prognosis, especially if delta band power is present in the contralateral hemisphere[66]. Conversely, more balanced high-frequency activity between hemispheres indicates a better functional prognosis.

Therefore, the persistence of slow activity and hemispheric asymmetry serves as a marker of greater post-stroke damage and poor prognosis.

Neurophysiologic Changes During the Chronic Phase of Stroke:

In the chronic phase of vascular insult, the natural progression involves the formation of a glial scar. Neural network reorganization continues to promote functional recovery during this stage, although its effectiveness diminishes over time. However, the remodelling of neural circuits might also lead to detrimental effects, including the consolidation of disrupted communication among neural networks, serving as a potential mechanism for cognitive deficits after stroke.

Perfusion imaging during the chronic phase reveals persistent hypoperfusion in the area surrounding the ischemic core. Research by Walenski et al. indicated no significant changes in tissue perfusion over time, even in patients undergoing successful rehabilitation[68]. Hypoperfusion in areas adjacent to the ischemic lesion has also been linked to the clinical status of aphasic patients[69]. These findings suggest that alterations in post-ischemic perfusion tend to endure in perilesional areas, and cerebrovascular reactivity may not consistently improve over time. Instead, it is the remodelling process that drives recovery.

EEG Studies:

EEG proves to be a valuable tool for longitudinally observing stroke. Alterations in the slow band, typically present in the EEG of stroke patients, consistently show improvement from the subacute to the chronic phase in patients experiencing good recovery. Changes in the 1/f properties of the EEG spectrum are sensitive to stroke evolution from the subacute to the chronic phase, with varying degrees of clinical correlation[70].

As mentioned earlier, patients with higher inter hemispheric imbalance in the acute stage generally have a worse prognosis. The persistence of higher Brain Asymmetry Index (BSI) values in the subacute and chronic stages remains a biomarker

of poor functional recovery, particularly concerning the motor system[70].

Finally, EEG connectivity appears to be locally impaired in chronic stroke, with significant modifications in connectivity observed from the sub-acute to the chronic stage. In the chronic phase, the reduction of beta band (12.5–30.0 Hz) oscillatory activity in the motor cortex serves as an index of motor impairment.

Hyponatremia and its Role in Acute Ischaemic Stroke:

Hyponatremia, defined as a serum sodium level below135 mEq/L, is a common electrolyte abnormality observed in patients with acute ischemic stroke. The presence of hyponatremia in the setting of acute ischemic stroke has been recognized as an important prognostic factor, with significant implications for patient outcomes.

The pathophysiology underlying the development of hyponatremia in acute ischemic stroke is multifactorial. The ischemic insult to the brain can lead to the release of various neuropeptides, such as antidiuretic hormone (ADH), which can stimulate water retention and cause dilutional hyponatremia. Additionally, the disruption of the hypothalamic-pituitary-adrenal axis and the release of inflammatory mediators can further contribute to the development of hyponatremia[12].

Prevalence and Incidence of Hyponatremia in Acute Ischemic Stroke:

Hyponatremia is a relatively common electrolyte abnormality observed in patients with acute ischemic stroke. The reported prevalence of hyponatremia in this patient population varies widely, ranging from 10% to 40% in different studies[11].

The incidence of hyponatremia in acute ischemic stroke can also vary depending on the timing of assessment and the study population. Some studies have reported that incidence of hyponatremia is higher during the acute phase of the stroke, with up to 30% of patients developing the electrolyte imbalance within the first few days of the event. However, the incidence may decrease over time as the patient's condition stabilizes and fluid and electrolyte homeostasis is restored.

The wide range in the reported prevalence and incidence of hyponatremia in acute ischemic stroke can be attributed to several factors, including[71]:

1. Differences in study populations: The characteristics of the patient population, such as age, co morbidities, and stroke severity, can influence the likelihood of developing hyponatremia.
2. Variations in diagnostic criteria: The definition of hyponatremia and the thresholds used to identify the condition may vary across different studies.
3. Timing of assessment: The prevalence and incidence of hyponatremia may differ depending on whether it is assessed at admission, during the acute phase, or throughout the hospital stay.
4. Management practices: The fluid and electrolyte management strategies employed in the acute care setting can impact the development and persistence of hyponatremia.

Understanding the prevalence and incidence of hyponatremia in acute ischemic stroke is crucial, as it highlights the importance of routine electrolyte monitoring and the need for early recognition and management of this common electrolyte abnormality.

Pathophysiology of Hyponatremia in Acute Ischemic Stroke:

The development of hyponatremia in patients with acute ischemic stroke is a complex and multifactorial process, involving various physiological and pathological mechanisms.

Role of Antidiuretic Hormone (ADH):

One of the primary mechanisms underlying hyponatremia in acute ischemic stroke is the release of antidiuretic hormone (ADH), also known as vasopressin. The ischemic insult to the brain can lead to the activation of the hypothalamic-pituitary-adrenal axis, resulting in the increased secretion of ADH from the posterior pituitary gland[72].

ADH plays a crucial role in water homeostasis by promoting water reabsorption in the kidney's distal tubules and collecting ducts. In the setting of acute ischemic stroke, the excessive release of ADH can lead to water retention, dilution of the extracellular fluid, and a subsequent decrease in serum sodium levels, resulting in hyponatremia.

The specific brain regions affected by the ischemic stroke can also influence the degree of ADH secretion. Ischemic damage to the hypothalamus or the pituitary gland, which are responsible for ADH regulation, can further exacerbate the dysregulation of ADH and contribute to the development of hyponatremia.

Disruption of Fluid and Electrolyte Homeostasis:

In addition to the role of ADH, acute ischemic stroke can also disrupt the normal fluid and electrolyte homeostasis through other mechanisms. The ischemic injury to the brain can impair the proper functioning of the hypothalamic-pituitary-adrenal

axis, leading to the dysregulation of various hormones involved in fluid and sodium balance, such as cortisol and aldosterone.

Furthermore, the inflammatory response triggered by the ischemic insult can also contribute to the development of hyponatremia. There lease of inflammatory mediators, such as cytokines and chemokines, can interfere with the normal renal handling of sodium and water, further exacerbating the electrolyte imbalance[71].

Co-morbidities and Medications:

Patients with acute ischemic stroke often have underlying comorbidities, such as heart failure, liver disease, or renal dysfunction, which can independently predispose them to the development of hyponatremia. These comorbidities can impair the body's ability to maintain fluid and electrolyte homeostasis, increasing the risk of hyponatremia in the setting of an acute ischemic event.

Additionally, certain medications commonly used in the management of acute ischemic stroke, such as diuretics, antidepressants, and anti-epileptic drugs, can also contribute to the development of hyponatremia. These medications can interfere with the normal regulation of sodium and water balance, further increasing the risk of electrolyte imbalances in this patient population.

Understanding the complex pathophysiological mechanisms underlying the development of hyponatremia in acute ischemic stroke is crucial for the effective management and prevention of this electrolyte abnormality, as well as for recognizing its potential impact on patient outcomes.

Impact of Hyponatremia on Clinical Outcomes in Acute Ischemic Stroke:

The presence of hyponatremia in patients with acute ischemic stroke has been consistently associated with poorer clinical outcomes, including increased mortality, functional impairment, and the risk of various complications.

Mortality

Numerous studies have investigated the impact of hyponatremia on mortality in patients with acute ischemic stroke. Specifically, the pooled analysis revealed that patients with hyponatremia had a 2.5-fold increased risk of mortality compared to those without hyponatremia. This increased risk of mortality associated with hyponatremia has been consistently reported across multiple studies, highlighting the prognostic significance of this electrolyte abnormality in the context of acute ischemic stroke[73].

Functional Outcomes

In addition to the impact on mortality, hyponatremia in acute ischemic stroke has also been linked to poorer functional outcomes.

The association between hyponatremia and poorer functional outcomes has been further corroborated by other studies, which have shown that patients with hyponatremia are more likely to have reduced independence in activities of daily living, impaired cognitive function, and a higher risk of long-term disability following an acute ischemic stroke.

Complications and Length of Stay

Hyponatremia in acute ischemic stroke has also been associated with an increased risk of various complications and a prolonged length of hospital stay[73].

Hyponatremia has been linked to a higher incidence of neurological complications, such as seizures, cerebral oedema, and further neurological deterioration. These complications can directly contribute to the worsening of the patient's clinical condition and impair the recovery process.

Moreover, hyponatremia has been associated with an increased risk of non-neurological complications, including respiratory distress, electrolyte imbalances, and derangements. These complications can further complicate the management of patients with acute ischemic stroke and prolong their hospital stay[71].

Several studies have reported that patients with hyponatremia in the setting of acute ischemic stroke tend to have longer hospital stays compared to those without hyponatremia. The increased length of stay may be a consequence of the higher incidence of complications, the need for more intensive monitoring and management, and the overall slower recovery trajectory associated with hyponatremia.

The mechanisms by which hyponatremia adversely affects the prognosis of acute ischemic stroke are not fully understood, but several proposed pathways have been suggested. Hyponatremia can lead to cerebral oedema, which can exacerbate the initial ischemic injury and contribute to further neurological deterioration. Additionally, hyponatremia may serve as a marker of the underlying severity of the ischemic insult and the patient's overall health status, which can influence the clinical course and recovery.

Severity and Timing of Hyponatremia

The severity and timing of hyponatremia in the setting of acute ischemic stroke may also have implications for patient prognosis.

Severity of Hyponatremia:

The degree of hyponatremia has been shown to be an important factor in predicting clinical outcomes. Severe hyponatremia, typically defined as a serum sodium level below 125 mEq/L, has been associated with a poorer prognosis compared to mild or moderate hyponatremia.

Studies have reported that patients with severe hyponatremia have a higher risk of mortality, a greater likelihood of developing complications, and a longer hospital stay compared to those with milder forms of hyponatremia. The severity of hyponatremia may reflect the underlying pathophysiological processes and the degree of disturbance in fluid and electrolyte homeostasis, which can contribute to the worsening of the patient's clinical condition[11].

Timing of Hyponatremia:

The timing of when hyponatremia develops in the course of acute ischemic stroke may also have prognostic implications. Some studies have suggested that develops early in the course of the stroke, particularly within the first few days, maybe associated with a poorer prognosis compared to hyponatremia that develops later.

Early-onset hyponatremia may be more closely linked to the acute ischemic insult and the associated disruption of neuroendocrine and fluid-electrolyte regulatory mechanisms. In contrast, hyponatremia that develops later in the course of the stroke may be influenced by other factors, such as the management of fluid and electrolyte balance, the presence of complications, or the development of comorbidities.

It is important to note that the temporal relationship between hyponatremia and clinical outcomes in acute ischemic stroke is not always straightforward, and the interplay between the severity and timing of hyponatremia can be complex. Careful monitoring and timely management of hyponatremia, regardless of the timing of its onset, maybe crucial in optimizing patient outcomes.

Management Considerations for Hyponatremia in Acute Ischemic Stroke:

The management of hyponatremia in patients with acute ischemic stroke requires a multifaceted approach, considering the underlying pathophysiology, the severity of the electrolyte imbalance, and the potential risks associated with the correction of hyponatremia[71].

Identification and Monitoring

The early recognition and monitoring of hyponatremia are essential in the management of acute ischemic stroke. Routine serum sodium level assessment at admission and during the course of hospitalization can facilitate the timely identification of this electrolyte abnormality.

It is important to note that the presence of hyponatremia, particularly in the acute phase of the stroke, may serve as a valuable prognostic indicator, and its recognition can guide the management and monitoring of the patient's condition.

Fluid and Electrolyte Management

The mainstay of management for hyponatremia in acute ischemic stroke involves the careful correction of the electrolyte imbalance, while considering the potential risks associated with rapid sodium correction.

In general, the management of hyponatremia in this setting should aim to address the underlying cause, such as the excessive release of ADH or the disruption of fluid- electrolyte homeostasis. This may involve the use of fluid restriction, the administration of hypertonic saline, or the use of diuretics, depending on the specific circumstances and the severity of the hyponatremia.

It is crucial to avoid rapid correction of hyponatremia, as this can lead to the development of osmotic demyelination syndrome, a serious neurological complication that can result in permanent brain damage. The recommended rate of sodium correction is typically no more than 8-12 mEq/L per day, with close monitoring of the patient's serum sodium levels and neurological status[71].

Management of Underlying Conditions

Addressing the underlying conditions that may contribute to the development of hyponatremia is also an important aspect of the management approach. This may include the management of comorbidities, such as heart failure, liver disease, or renal dysfunction, as well as the optimization of medication regimens that may be contributing to the electrolyte imbalance.

By addressing the underlying causes and carefully managing the electrolyte abnormality, clinicians can aim to mitigate the adverse effects of hyponatremia and potentially improve the clinical outcomes of patients with acute ischemic stroke.

Prognostic Implications and Risk Stratification

The recognition of hyponatremia as an important prognostic factor in acute ischemic stroke has led to the development of risk stratification models and the integration of this electrolyte abnormality into clinical decision-making processes.

Risk Stratification Models:

Several studies have attempted to incorporate hyponatremia into risk assessment models for predicting outcomes in patients with acute ischemic stroke. These models often include hyponatremia as one of the variables, along with other clinical, laboratory, and radiological parameters, to provide a more comprehensive assessment of the patient's prognosis.

For example, the PLAN score, which stands for "Pressure, Level of consciousness, Age, and Number of comorbidities," has been validated and shown to improve the prediction of functional outcomes and mortality in patients with acute ischemic stroke when hyponatremia is included as an additional parameter.

By incorporating hyponatremia into these risk stratification models, clinicians can better identify patients at a higher risk of poor outcomes and guide the implementation of more intensive monitoring, targeted interventions, and appropriate resource allocation[72-78].

Clinical Decision-Making

The recognition of hyponatremia as a prognostic factor in acute ischemic stroke has also influenced clinical decision-making and management strategies. Clinicians may consider the presence and severity of hyponatremia when making decisions regarding the intensity of care, the aggressiveness of treatment, and the goals of therapy.

For instance, the presence of severe or persistent hyponatremia may prompt clinicians to consider more aggressive management approaches, such as the use of hypertonic saline or the involvement of a specialist in electrolyte management. Additionally, the recognition of hyponatremia as a poor prognostic factor may lead to more careful consideration of the patient's goals of care and the potential impact on long-term outcomes.

By integrating the assessment and management of hyponatremia into the overall care of patients with acute ischemic stroke, clinicians can strive to optimize the patient's clinical course, minimize the risk of complications, and improve the likelihood of favourable outcomes.

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Case Report

Challenges Enroute to a Foreign Body Removal via Rigid Bronchoscopy in an 8-month-old Infant

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ABSTRACT

An 8-month-old baby presented with symptoms respiratory distress and history of aspiration of food particle. Physical examination and investigations revealed that the left main bronchus was obstructed due the foreign body being lodged in its distal part. The foreign body was carefully retrieved by direct bronchoscopy in Emergency OT following which the condition of child drastically improved.

KEYWORDS: Foreign body, Tracheobronchial foreign body, Rigid bronchoscopy, Obstructive emphysema

PRESENTATION OF THE CASE

An 8-month-old baby presented with dyspnea for one day at the ENT OPD. Attendants of the patient gave history of feeding watermelon fruit to the baby who was crying previously, following which the patient apparently developed difficulty in breathing.

The patient displayed refusal to feeds and labored breathing.

On examination use of accessory respiratory muscles, an increased respiratory rate and features of labored breathing were noted. On percussion hyper resonant note was elicited on the left lung fields. Auscultation revealed decreased breath sounds and decreased vocal resonance on left lung fields.

Chest x ray revealed hyperluscency in left lung fields. Midline appeared to have shifted to right side [Figure 1]. HRCT chest revealed soft tissue density 8mm * 3mm in distal left main bronchus with hyperinflation of left lung and diffuse air trapping noted [Figures 2, 3, 4 and 5].

Patient was planned for diagnostic cum therapeutic rigid bronchoscopy under general anaesthesia. Consent explaining the procedure, complications and post operative management including possible ventilatory support was taken. Most importantly, 'on table death possibility' consent was also explained and video documented.

PROCEDURE

After general anesthesia was given, position of flexion at neck-thorax and extension at atlanto-occipital junction given.

Storz Rigid bronchoscopes of the sizes 3.5 and 4.5, led white light source, light carrier, straight blade pediatric macintosh laryngoscopes were used.

Upper end of endotracheal tube was used to connect to the ventilating port of rigid bronchoscope and connected to pediatric anesthesia circuit.

Patient was ventilated till oxygen saturation reached 100%. Macintosh laryngoscope used to visualize the larynx and guide the rigid bronchoscope.

Initially 4.5 sized rigid bronchoscope used which could not negotiate the glottis. Following which 3.5 sized rigid bronchoscope was used. The 3.5 sized bronchoscope was so narrow that it did not allow passage of optical foreign body retrieval forceps. Hence a non-optical foreign body forceps was used to remove the foreign body. Even with normal forceps the procedure was almost blind as the lumen of the 3.5 sized scope is very narrow. A positive pressure ventilation with intermittent apnea technique used. Sometimes during the procedure, the entire bronchoscope had to be removed as the ventilation of the opposite lung was inadequate at times. This led to quick desaturation leading to a cycle of endotracheal intubation, ventilation, saturating unto 100% and handing over to surgeon.

Finally, after some attempts foreign body was visualized from left main bronchus and retrieved intact [Figure 8]. Following which breath sounds and ventilation of left lung drastically improved. The oxygen saturation also started to remain more than 98% on spontaneous ventilation.

Five hours postoperatively the signs of distress were notably absent. Child appeared calm and more playful. Improved vocal resonance and breath sounds were noted on left lung fields. Post operative x ray showed shift of cardia and trachea towards normal (fig 6), improved broncho-vascular markings and decreased luscency suggesting the air trapping was relieved. The patient was discharged the following day.

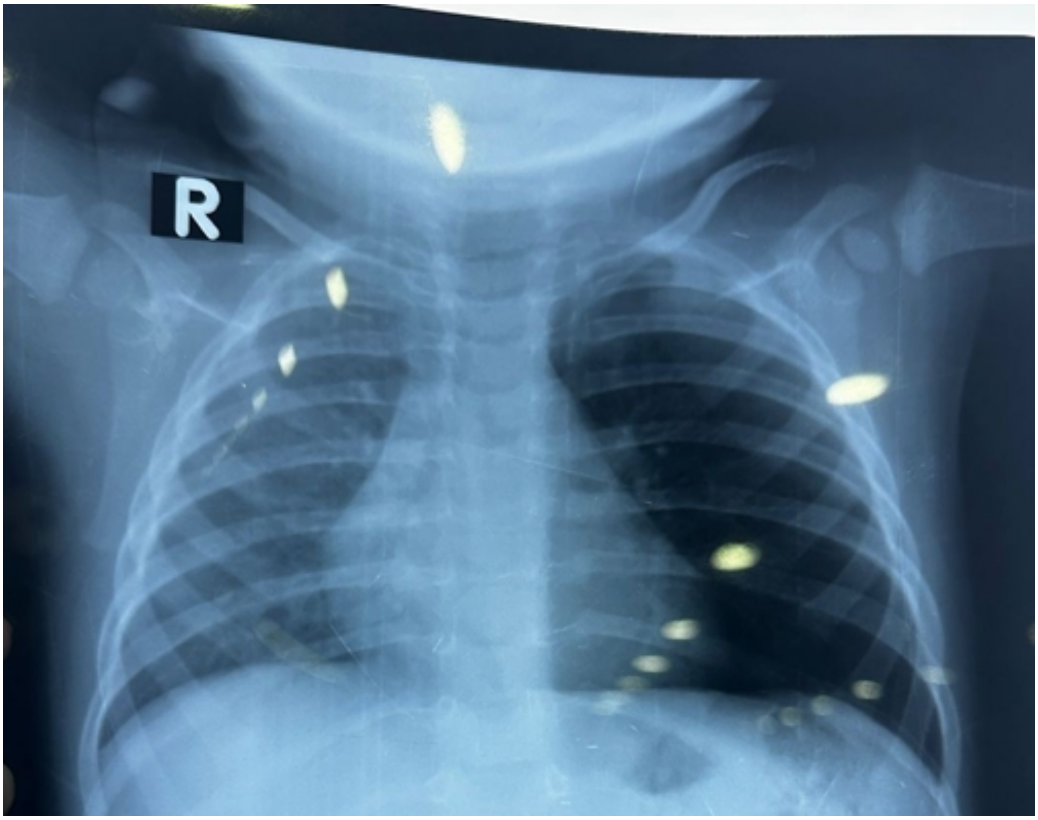


Figure 1: X ray showing Obstructive Emphysema on the Left Side and Tracheal Deviation

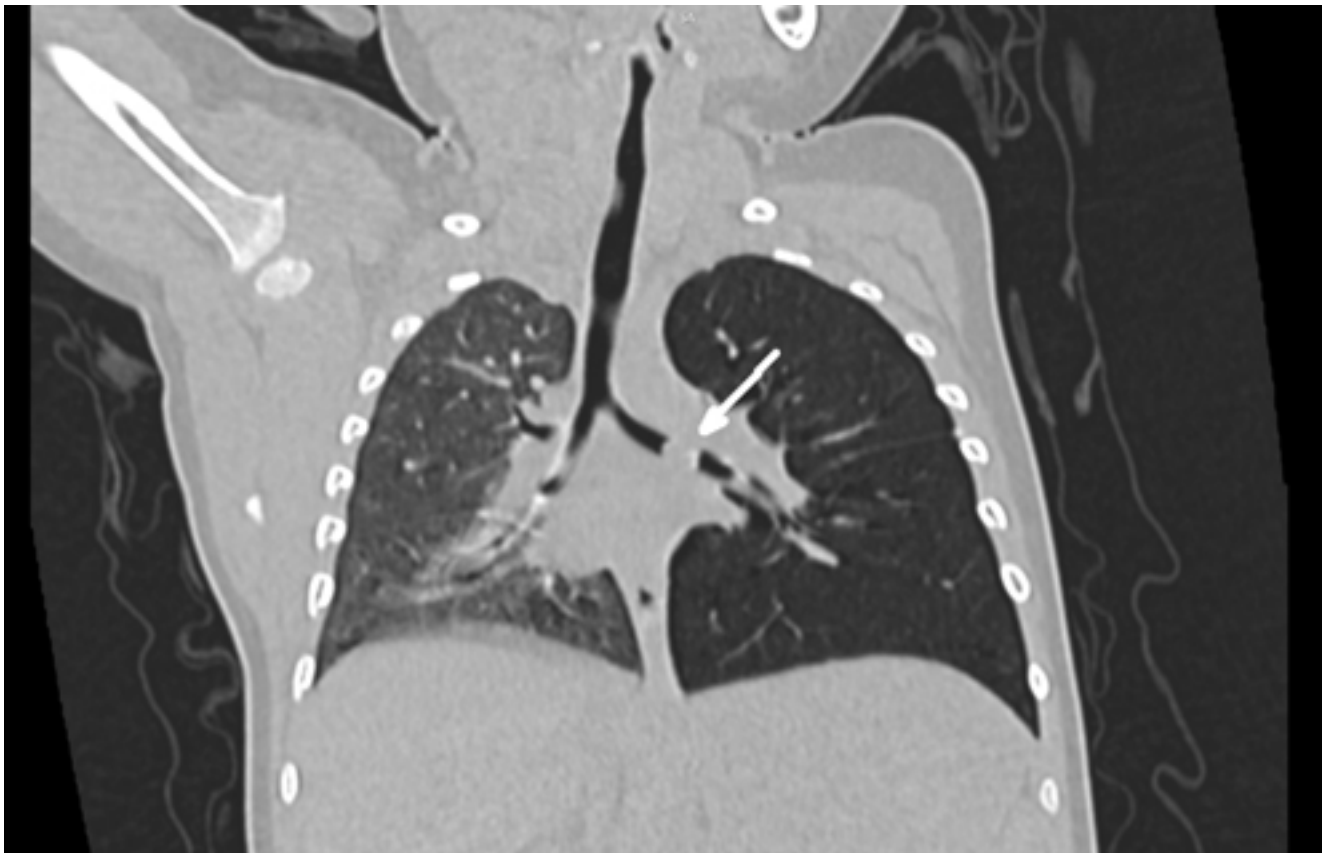


Figure 2: CT Chest showing Foreign Body in Left Main Bronchus

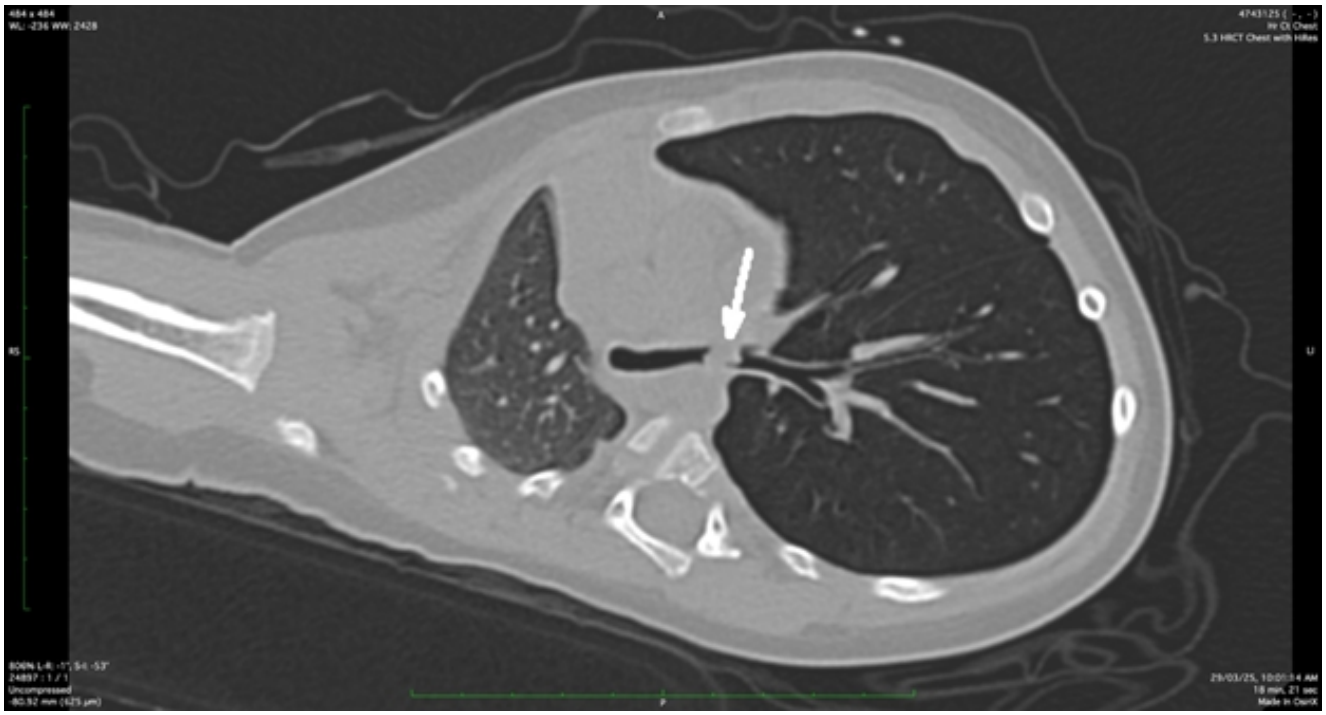


Figure 3: Axial View CT Chest showing Foreign Body in Left Main Bronchus and Obstructive Emphysema

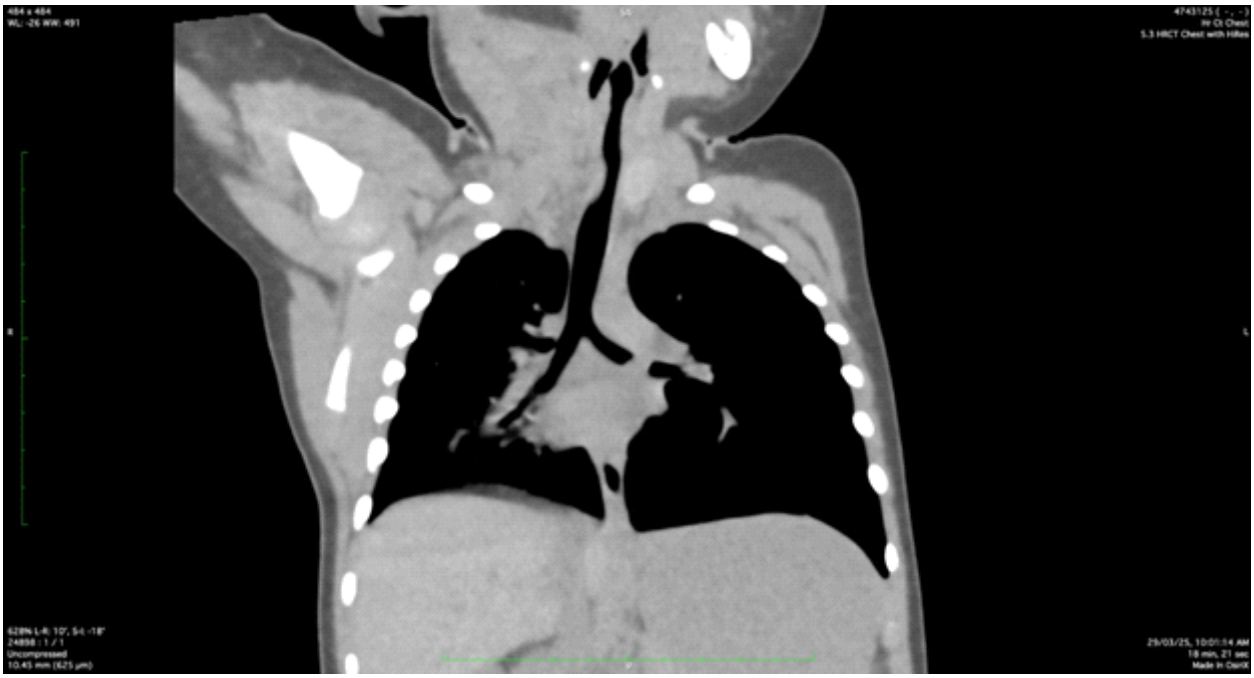


Figure 4: Coronal CT Chest showing Foreign Body in Left Main Bronchus

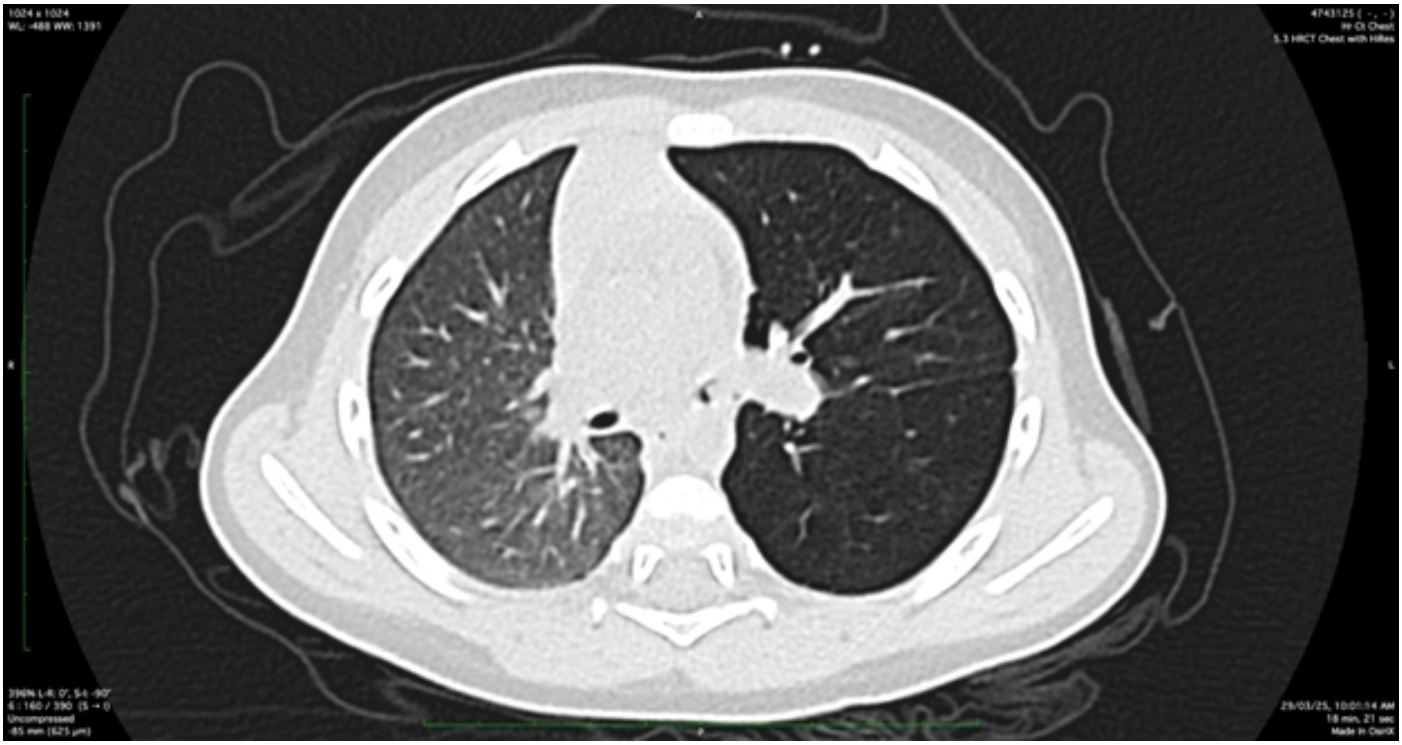
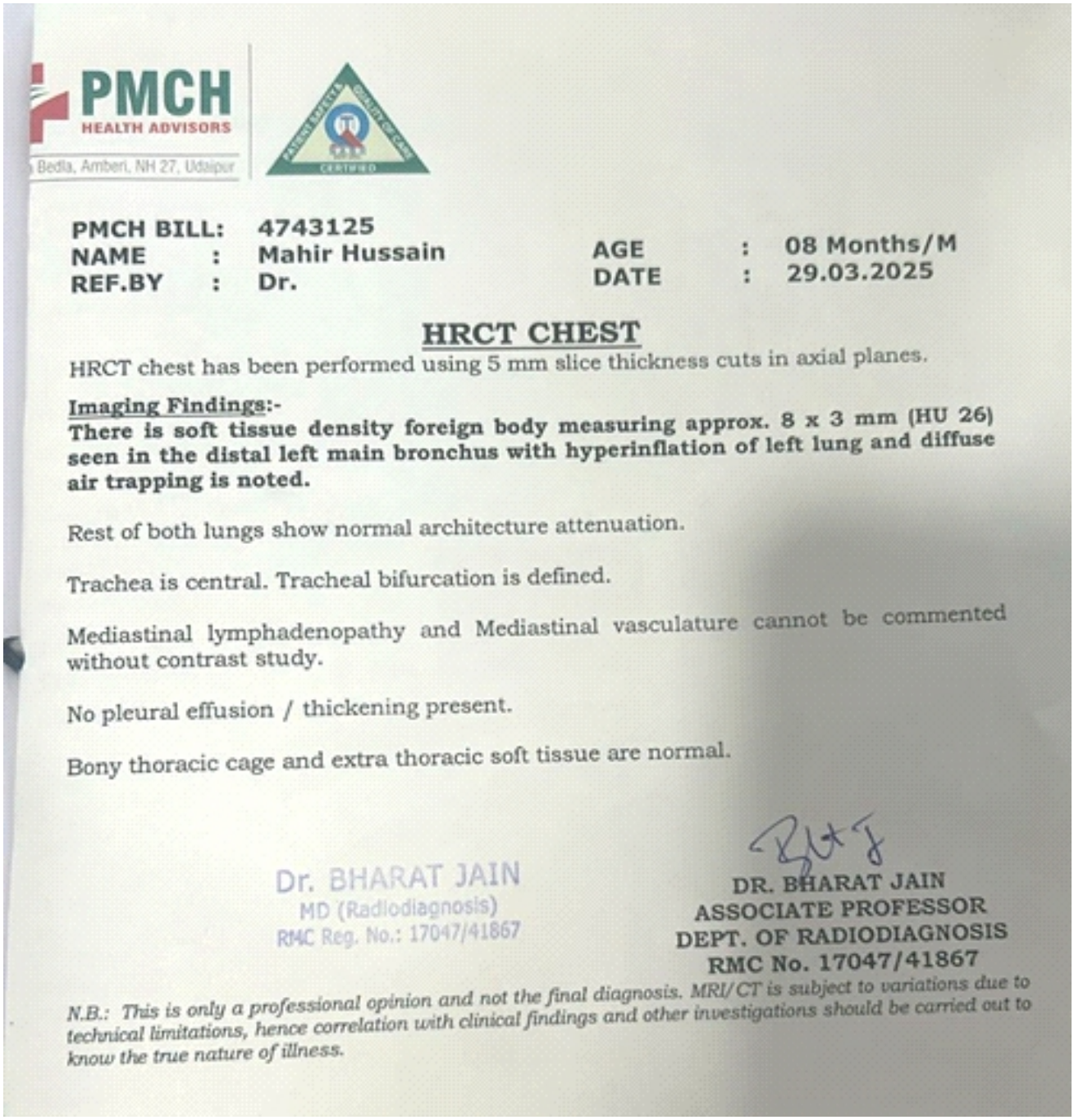


Figure 5: CT Chest showing Foreign Body in Left Main Bronchus

Figure 6: Post-operative X-ray shows Normal Left Lung Fields



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REF.BY : Dr.
AGE : 08 Months/M
DATE : 29.03.2025

HRCT CHEST

HRCT chest has been performed using 5 mm slice thickness cuts in axial planes.

Imaging Findings:-
There is soft tissue density foreign body measuring approx. 8 x 3 mm (HU 26) seen in the distal left main bronchus with hyperinflation of left lung and diffuse air trapping is noted.

Rest of both lungs show normal architecture attenuation.

Trachea is central. Tracheal bifurcation is defined.

Mediastinal lymphadenopathy and Mediastinal vasculature cannot be commented without contrast study.

No pleural effusion / thickening present.

Bony thoracic cage and extra thoracic soft tissue are normal.

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N.B.: This is only a professional opinion and not the final diagnosis. MRI/CT is subject to variations due to technical limitations, hence correlation with clinical findings and other investigations should be carried out to know the true nature of illness.

Figure 7: HRCT Report

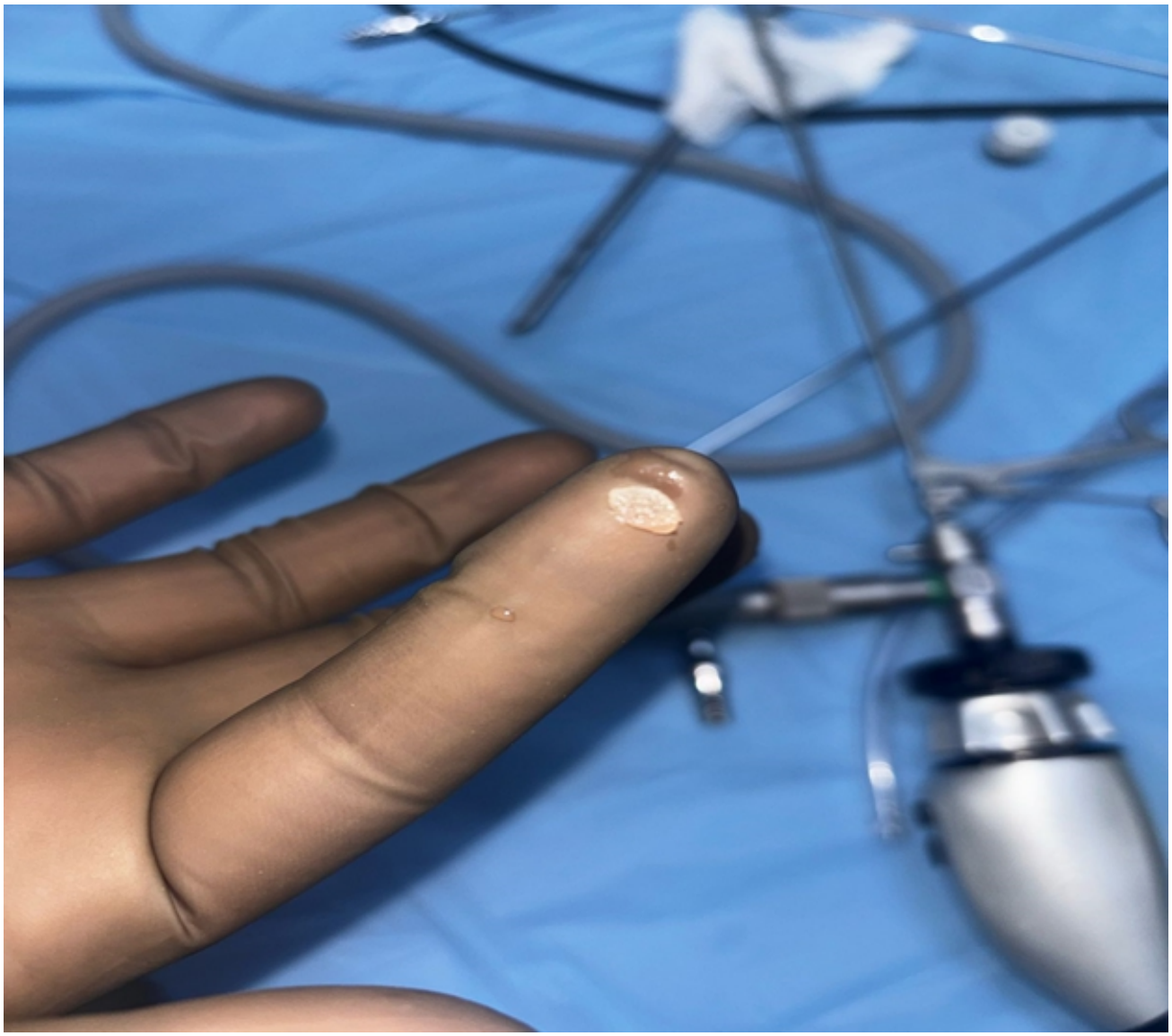

Figure 8: Post-operative Picture shows Foreign Body Retrieved from Left Bronchus

DISCUSSION

Gustav Killian is considered as the first surgeon to have performed rigid bronchoscopy in 1897. Incidentally he performed bronchoscopy using a rigid esophagoscope to remove a pig bone from bronchus. Tackling a case of pediatric foreign body in the operation theatre gives its fair share of jitters to the operating surgeon and anesthetist involved. Often this surgery involves adrenaline packed atmosphere in the O.R as this procedure mandates each and every personnel tackling this emergency to be at their best of reflexes.

The anesthetist and the operative surgeon juggle taking turns with precision to ventilate the lungs and visualize the foreign body respectively to ultimately retrieve it. This sharing of the airway space makes it more complicated.

Foreign body of the tracheobronchial pathway comprises one of the leading causes of death in pediatric patients aged 1-3 years is due to foreign body lodged in airway. Some of these cases could be due the inability to reach emergency department and O.R on time.

Most of the patients of tracheobronchial foreign bodies present with cough and dyspnea ranging till stridor[4]. However, some patients are asymptomatic on presentation. Chronic foreign bodies usually present with cough not relieving on medication. So, for a child with unrelenting cough a suspicion of tracheobronchial foreign body must be at the back of pediatrician's mind.

Most frequently the radiological finding encountered is of obstructive emphysema or an air trapping picture because of the ball valve mechanism. Other radiological features may range from collapse of segment, consolidation or rarely normal skiagram. Consolidation and a normal skiagram may have a long seated foreign body[5].

The surgeon ideally expects the patient's airway to be adequately ventilated, adequate depth of anesthesia and minimal secretions while navigating the airway. Some surgeons prefer spontaneous ventilation over positive pressure ventilation during this procedure. Some studies noted less chance of dislodging of foreign body further distally, less chances of pneumothorax, laryngospasm or arrythmias in perioperative periods. Even the disruption of breathing is absent in cases of spontaneous ventilation[1]. Whereas when a foreign body is in the distal part of tracheobronchial tree, positive pressure ventilation and intermittent apnea technique is used.

Cases of injury to tracheobronchial mucosa especially when operating using smaller bronchoscopes is common due to the small working channels. This can be mitigated to some extent by using or applying masking tapes on the retrieving forceps at lengths of bronchoscope and successively at every 3mm interval[2]. If at all a forceps accidentally grasps mucosa and is stuck, gentle closing of the forceps and retrieving of the forceps must be done. Some institutions have the optical forceps which likely may mitigate injury to tracheobronchial mucosa.

Vegetative foreign bodies like peanuts, cashew nut pieces, walnut pieces, areca nut are found to be commonly found in children generally aged less than 4 years of age. However older children being more curious often are found with plastic toys as foreign bodies in bronchus[3]. If a sharp foreign body like a pin in stuck in the mucosa, it must be gently dislodged and carefully retrieved.

After the procedure of bronchoscopy and foreign body retrieval some complications may occur. They may vary from simple bronchospasm, post operative bleeding or even bronchopneumonia.

CONCLUSION

Tracheo-bronchial foreign bodies consistently remain as one of the dire emergencies involving the pediatric age group. In managing this emergency there must be a well-orchestrated team effort while tackling this situation.

The possibility of tracheobronchial foreign must be kept in mind in cases of unrelenting cough.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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Case Series

Lightening the Load of Maxillary Atrophic Ridges: A Hollow Denture (Case Series)

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ABSTRACT

The core tenets of complete denture treatment are retention, stability, and support with acceptable aesthetics and good speech. For patients with specific anatomical traits such as highly resorbed ridges, long lip length, and increased interridge distance, the principles are often compromised with conventional dentures. The maxillary denture fabricated in such patients are bulky in nature which further compromise its retention. Such clinical situations necessitate the fabrication of a hollow complete denture to reduce the weight of the prosthesis and increase retention. Moreover, the reduced material volume contributes to more life-like usage of the maxillary complete denture with improved patient satisfaction. This article presents several ways of crafting hollow dentures with the aim of preserving the underlying tissues, enhancing denture performance, and minimizing bone resorption.

KEYWORDS: Hollow denture, Inter ridge distance, Light weight denture, Residual ridge resorption

INTRODUCTION

Rehabilitation of completely edentulous maxillary and mandibular arches comprise several treatment strategies. A patient's age, systemic disorders, financial situation, and other variables are taken into consideration when determining those treatment plans. For edentulous maxillary and mandibular ridges, a complete denture is one such alternative. When dentures meet these requirements, function and appearance are restored while also ensuring patient comfort. A complete denture must be fabricated in a number of processes in order to get the intended outcomes. "No step-in denture construction should be stopped short of perfection yet many dentures are worn, which have imperfections built into them, provided they have peripheral seal sufficient to hold them in place"[1,2].

After teeth are extracted, a complex biophysical process known as residual ridge resorption frequently occurs. Ridge atrophy is most dramatic during the 1st year after tooth loss followed by a slower but more progressive rate of resorption thereafter. Increase interridge space may result in a heavy maxillary complete denture that may compound the poor denture-bearing ability of the tissues and lead to decreased retention and stability. Therefore, by making a hollow cavity inside the maxillary complete denture, its weight can be decreased in patients with significant inter-ridge spaces. The rationale for choosing hollow dentures

are as they help in managing the existence of increased inter ridge distance and reduce the heaviness of the denture base. Numerous materials have been used to build a 3D hollow space within a denture such as dental stone, cellophane wrapped asbestos, silicone putty, modelling clay, thermocol, play dough, light-body coated gauge, salt, or glycerine soap during processing[1,3,4].

This case report describes three techniques for fabrication of a hollow maxillary complete denture in a patient with resorbed maxillary and mandibular ridges and increased interridge distance using glycerine soap, alkaline salt and absorbable gelatine sponge.

CASE REPORTS

A. Case 1: Hollow Denture Using Glycerine Soap [Figure 1 a-i]

A 56-year-old male patient presented to the Department of Prosthodontics, Darshan Dental College and Hospital, Udaipur with a complaint of complete edentulism in both maxillary and mandibular arches. Patient was a denture wearer for the past 3 years and complained of looseness of maxillary denture. Past medical history was not significant. Thus, a conventional mandibular denture and maxillary hollow denture was fabricated.

a) The maxillary denture was constructed up to the trial denture stage using conventional method.
b) The waxed-up trial denture base was sealed to the master cast; duplicated using irreversible hydrocolloid (alginate) and then poured with dental stone.
c) A 1 mm thick thermoplastic sheet was used to create a template of the duplicated trial denture using a vacuum heat-press machine onto the duplicated cast.
d) The trial denture was then subsequently processed up to the wax burnout stage using conventional method.
e) The denture processing was carried out using two denture flasks with interconvertible lids.
f) To the master cast, two layers of baseplate wax were adapted in line with the peripheral extension of the cast. After that, it is transferred to the second flask and processed as usual.
g) Following deflasking, the template was positioned on the master cast, creating an index in the land area of the cast to serve as a seating reference. An endodontic file with a rubber stopper is used to quantify the distance between the template and the treated base.
h) The Polyvinylsiloxane putty was manipulated and shaped to conform the estimated configuration of the template, leaving 2–3 mm of space between the template and the spacer. Over the tooth portion of the denture, an extra 1 mm of clearance was kept.
i) With the putty spacer as reference, soap replica was modelled using Le Cron carver and the exact measurement was verified with Vernier's caliper.
j) The trial closure was performed using putty spacer, which was then removed from the flask. The mold space was visually inspected to ensure that the resin thickness was adequate around the entire hollow cavity.
k) Final closure is done with soap spacer filled into the mold space and acrylized conventionally.
l) After retrieval of the denture, two orifices were created on the distal aspect of the most posterior tooth in the denture base. Then, it is placed in the container of water for dissolution of soap. Devices such as cleaning brush and water spray were used to completely remove any remaining traces of soap. After being sealed with auto-polymerizing resin, the two orifices were evaluated for a water test.
m) The maxillary and mandibular dentures were inserted to the patient after final finishing and polishing.

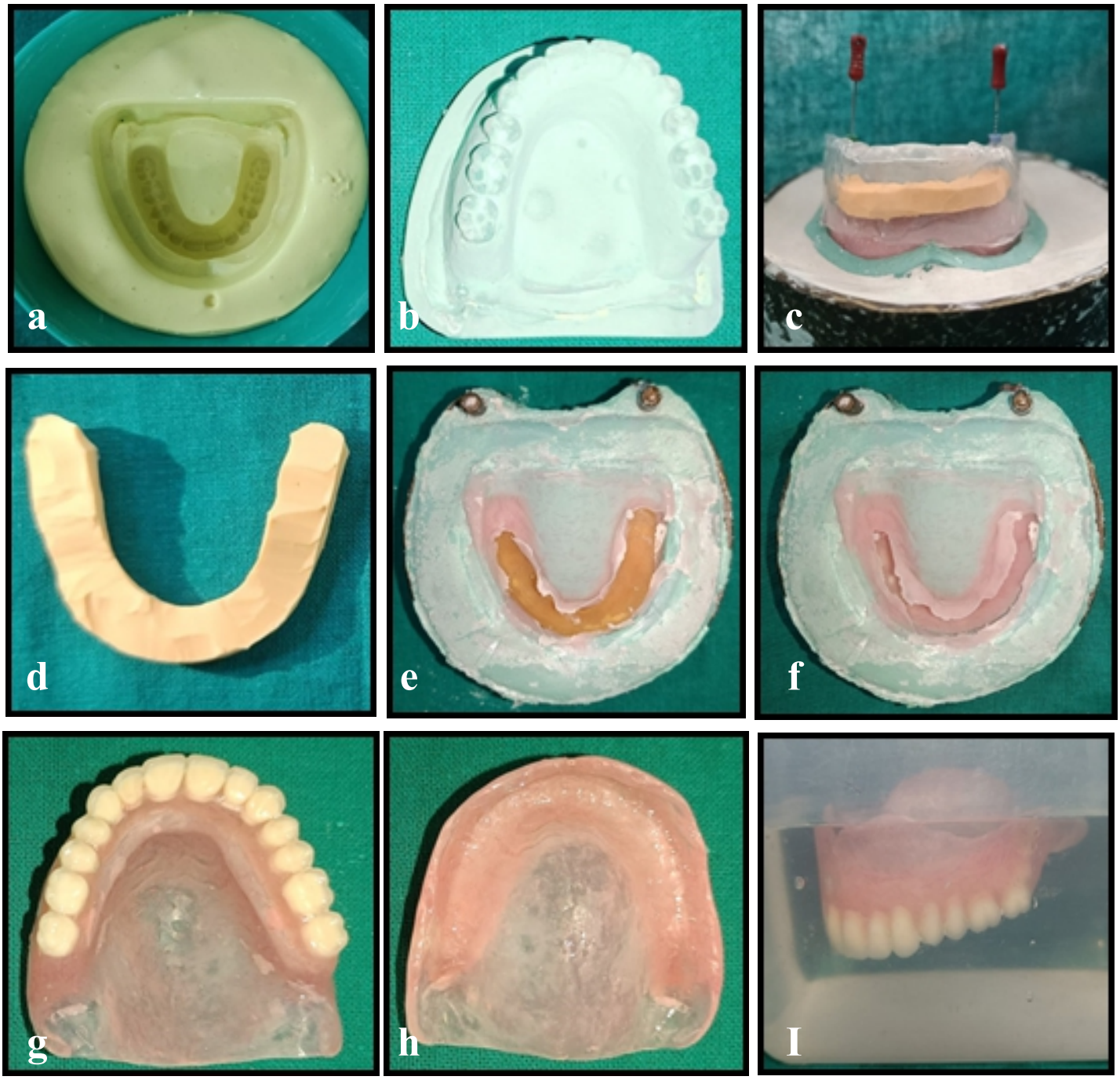

Figure 1: Hollow Denture Using Glycerine Soap
(a) Duplication of waxed up denture;
(b) 2mm thick polyethylene sheet pressed on the duplicate stone cast;
(c) Measuring the distance between the putty spacer and polyethylene sheet using endodontic file with rubber stopper;
(d) Putty spacer; (e) Space created with putty spacer;
(f) Glycerine soap placed in the hollow cavity; (g) Cameo surface; (h) Intaglio surface; (i) Water test

B. Case 2: Hollow Denture Using Absorbable Gelatine Sponge [Figure 2 a-i]

A 56-year-old male patient presented to the Department of Prosthodontics, Darshan Dental College and Hospital, Udaipur with chief complaint of difficulty in chewing and poor aesthetics. Patient was a denture wearer for the past 5 years and complained of attrition of denture teeth. Extra oral examination revealed patient was having long upper lip with drooped corners of mouth. Intra oral examination revealed severely resorbed edentulous ridges with increased inter-ridge distance. Thus, the treatment of maxillary hollow dentures is planned with a conventionally fabricated mandibular denture.

a) The maxillary denture was constructed similarly up to the preparation of the template of trial denture.
b) Instead of putty spacer as a reference, plastic straw was used and absorbable gelatine sponge of 1cm thickness was modelled using Le Cron carver.
c) The trial closure was achieved with a plastic straw and mold space was filled with gelatine sponge material in the final closure of the processing step.
d) The absorbable gelatine sponge was left inside the mold space and acrylization was carried out conventionally.
e) After retrieval of the denture, two orifices were created on the distal aspect of the most posterior tooth in the denture base. Then water spray was used to completely remove the gelatine sponge. After being sealed with auto-polymerizing resin, the two orifices were evaluated for a water test.
f) The maxillary and mandibular dentures were inserted to the patient after final finishing and polishing.

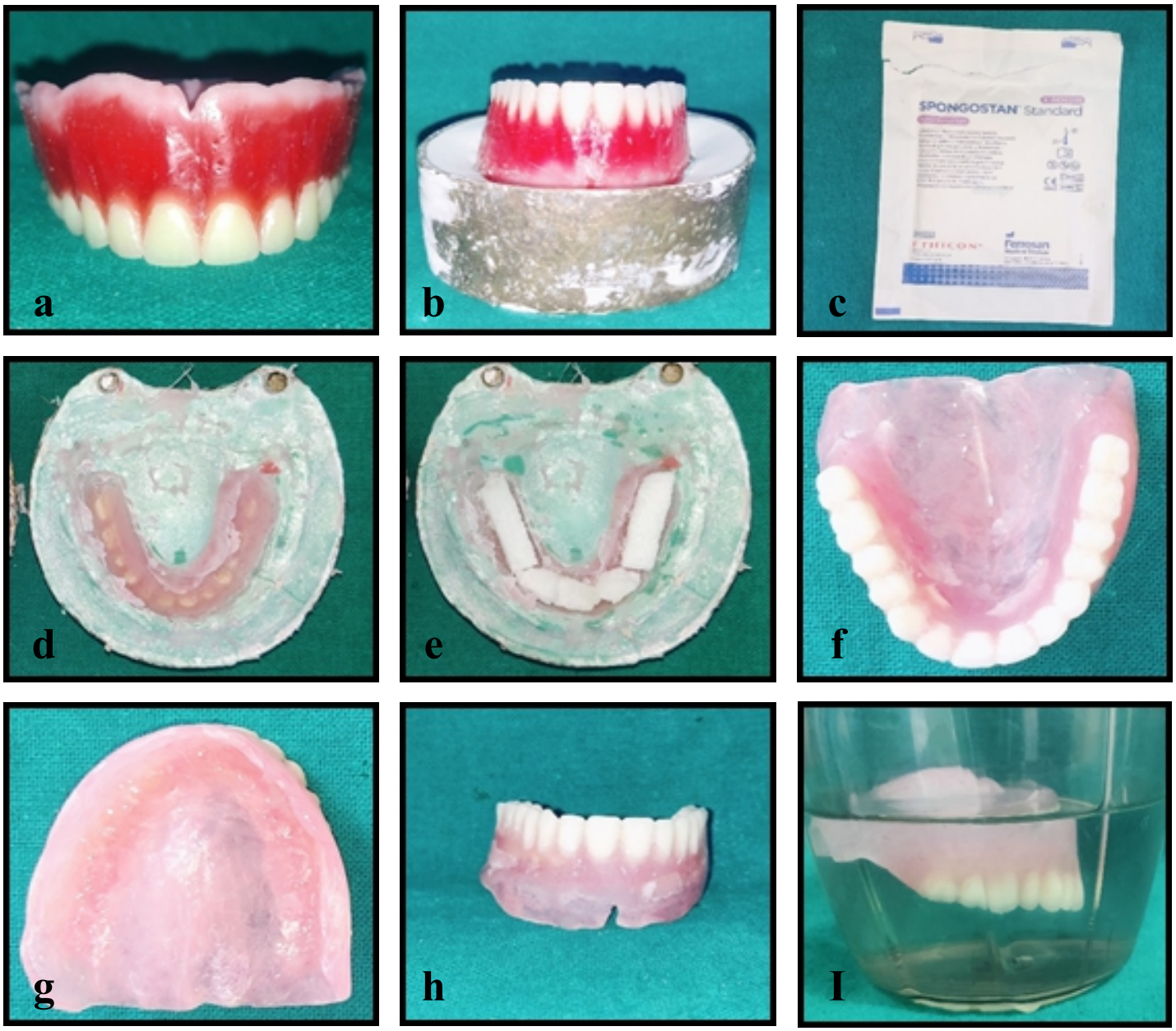

Figure 2: Hollow Denture Using Absorbable Gelatine Sponge (a) Waxed up maxillary denture; (b) Flasking; (c) Absorbable gelatine sponge; (d) Space created with straw; (e) Gelatine sponge placed; (f) Cameo surface; (g) Intaglio surface; (h) Hollow denture; (i) Water test

C. Case 3: Hollow Denture Using Alkaline Powder (Papad Khar) [Figure 3a-i]

A 51-year-old male patient reported to the Department of Prosthodontics, Darshan Dental College and Hospital, Udaipur with a chief complaint of looseness of both upper and lower dentures and desired the replacement of the same. His history revealed that, he had been edentulous for 15 years and had been wearing dentures for 14 years. The intra-oral examination revealed a narrow and constricted U-shaped flat palatal vault and moderately resorbed maxillary and mandibular ridges. The treatment plan decided for the patient was the fabrication of a hollow maxillary complete for better stability and retention.

a) The maxillary trial denture was flasked and dewaxed in the conventional manner.
b) Half of the heat cure PMMA (Trevalon, Dentsply India Pvt. Ltd., Gurgaon, India) in dough stage was positioned accurately over the dewaxed mould and then alkaline powder crystals were placed over it.
c) Above that, the remaining heat cure resin was packed and acrylization was carried out conventionally.
d) Cured denture was retrieved and 2 holes were made in the thickest palatal area.
e) All the alkaline powder crystals were removed by flushing water with the high-pressure syringe through the holes.
f) After making sure that all the alkaline powder crystals have been removed, the escape holes were closed with auto polymerizing resin (Trevalon, Dentsply India Pvt. Ltd., Gurgaon, India).
g) The hollow cavity seal was verified by immersing the denture in water, if no air bubbles are evident, an adequate seal is confirmed.
h) The dentures were inserted in the patient's mouth and instructions regarding care, hygiene and maintenance were given.

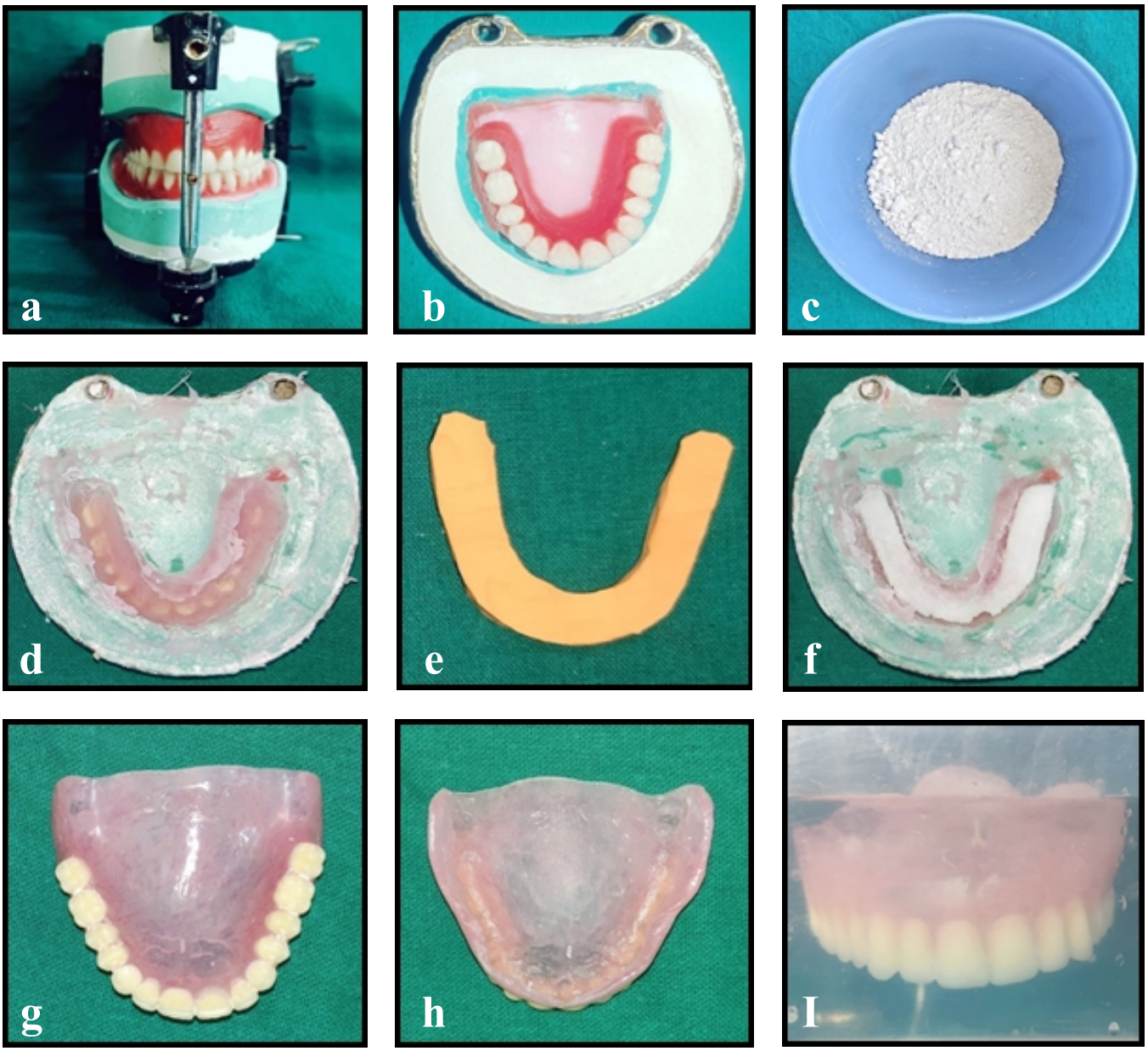

Figure 3: Hollow Denture Using Alkaline Powder (a) Waxed up denture; (b) Flasking; (c) Alkaline powder; (d) Space created with putty; (e) putty spacer; (f) Alkaline powder placed; (g) Cameo surface; (h) Intaglio surface; (i) Water test

DISCUSSION

The fundamental goal of prosthodontic rehabilitation is to restore the functional and aesthetic deficiencies. Tooth loss leads to residual ridge resorption which is a complex phenomenon driven by various anatomic, prosthetic, functional and metabolic factors. A reduced denture-bearing area with a significant inter-ridge void will result from extreme resorption of either ridge, which will impact the denture's overall stability, support, and retention. Hence, the best way is to rehabilitate them with reducing the weight of maxillary prosthesis which has been shown to be beneficial. This can be achieved by making the maxillary denture hollow[5,6].

Case 1 described in the presented case used a soap spacer with a high content of glycerine and other humectants in it, rendering it highly water-soluble compared to other soaps. According to previous studies, the primary benefits of employing glycerine soap spacer are its capacity to withstand high curing temperatures (glycerine has a boiling point of 290°C) and the fact that it doesn't obstruct the polymerization of heat-cured acrylic resin, leaving no residues inside the hollow cavity. Also, because the soap spacer is eventually removed leaving behind a clean hollow cavity, any concern regarding its biocompatibility in the oral cavity is dismissed. Fattore, Fine, and Edmonds[7] used a double flask method to reduce denture weight. The use of the double flask technique was cumbersome and more time-consuming, with increased cost as well.

The qualities of absorbable gelatine sponge, such as its low weight, ease of adaptability to any space, commercial availability, and non-adherence to acrylic resin, led to its application. This material has advantages over previously used material. Absorbable gelatine being a lightweight & Gamma sterilized sponge makes it biocompatible to use. Other advantage is that it may withstand high temperature[8].

Case 3 described has advantages over the previously described techniques. The alkaline powder being heat labile melt during the curing procedure and thorough flushing after curing results in no crystals remaining in the denture and preventing the time-consuming process of removing the spacer material, therefore preserving the denture's integrity. This technique of using alkaline powder crystals is simple to execute and utilizes a very cheap and easily available spacer material[9].

In cases 2 and 3, single-flask techniques had additional advantages. The thickness of the resin can be controlled by adapting an even thickness of putty index all around after measuring it with verniers calliper. In the end, this will guarantee an even resin depth to stop seepage and distortion when the flask is closed under pressure. The benefits of hollow dentures include a decrease in the excessive weight of the acrylic resin, which makes the prosthesis lighter and more pleasant for the patient[6].

CONCLUSION

The ideal way to treat a patient with a severely resorbed ridge and lengthy lips is with a hollow maxillary denture. It not only lessens the denture's weight but also its leverage action. This ultimately results in increased retention and stability and up to some extent it is also possible to preserve the existing residual alveolar ridge. The need for two identical flasks and the additional step of creating a permanent record base are eliminated by the single flask technique. It is therefore a straightforward, cost-effective, time-saving, and reliable method.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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New Drug Approvals

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
1.	Immunoglobulin A Nephropathy	Vanrafia (Atrasentan) Tablets	Novartis Pharma-ceuticals Corporation	Vanrafia (Atrasentan) is an Endothelin A receptor antagonist used for proteinuria reduction in primary immunoglobulin (IgA) nephropathy.	April 2, 2025
2.	Colorectal Cancer, Non Small Cell Lung Cancer, Glioblastoma Multiforme, Renal Cell Carcinoma, Cervical Cancer, Ovarian Cancer, Fallopian Tube Cancer, Peritoneal Cancer	Jobevne (Bevacizumab-nwgd) Injection	Biocon Biologics Ltd.	Jobevne (Bevacizumab-nwgd) is a vascular endothelial growth factor inhibitor biosimilar to Avastin used for the treatment of colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer.	April 9, 2025
3.	Schizophrenia	Mezofy (Aripiprazole) Oral Film	CMG Pharma-ceutical Co., Ltd.	Mezofy (Aripiprazole) is an oral film formulation of the approved atypical antipsychotic aripiprazole indicated for the treatment of schizophrenia in adult and paediatric patients ages 13 years and older.	April 15, 2025
4.	Nasopharyngeal Carcinoma	(Penpulimab-kcqx) Injection	Akeso, Inc.	Penpulimab-kcqx is a programmed death receptor-1 (PD-1)-blocking antibody for use in the treatment of advanced nasopharyngeal carcinoma	April 23, 2025

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
5.	Epidermolysis Bullosa	Journavx (Suzetrigine) Tablets - formerly VX-548	Abeona Therapeutics Inc.	Zevaskyn (Prademagene zamikeracel) is an autologous, cell sheet-based gene therapy for the treatment of patients with recessive dystrophic epidermolysis bullosa.	April 28, 2025
6.	Myasthenia Gravis	Imaavy (Nipocalimab -aahu) Injection	Johnson & Johnson	Imaavy (Nipocalimab-aahu) is a neonatal Fc receptor (FcRn) blocker used for the treatment of generalized myasthenia gravis.	April 29, 2025
7.	Migraine	Atzumi (Dihydroer-gotamine mesylate) Nasal Powder – formerly STS101	Satsuma Pharma-ceuticals, Inc.	Atzumi (Dihydroergotamine mesylate) is a nasal powder formulation of the ergotamine derivative Dihydroergotamine mesylate for the acute treatment of migraine.	April 30, 2025
8.	Ovarian Cancer	Avmapki Fakzynja Co-Pack (Avutometinib and Defactinib, co-packaged) Capsules/ Tablets	Verastem Oncology	Avmapki Fakzynja Co-Pack (Avutometinib and Defactinib, co-packaged) is a kinase inhibitor combination for the treatment of KRAS-mutated recurrent low-grade serous ovarian cancer.	May 8, 2025
9.	Non-small Cell Lung Cancer	Emrelis (Telisotuzumab vedotin-tllv) Lyophilized Powder for Injection - formerly Teliso-V	AbbVie Inc.	Emrelis (Telisotuzumab vedotin) is a first-in-class, c-Met protein directed antibody-drug conjugate for the treatment of non-squamous non-small cell lung cancer with high c-Met protein overexpression.	May 14, 2025

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
10.	Migraine, Cluster Headaches	Brekiya (Dihydroergotamine mesylate) Injection	Amneal Pharmaceuticals, Inc.	Brekiya (Dihydroergotamine mesylate) is a ready-to-use autoinjector presentation of the ergotamine derivative Dihydroergotamine mesylate for the acute treatment of migraine and the cluster headaches in adults.	May 14, 2025
11.	COVID-19	Nuvaxovid (COVID-19 Vaccine, Adjuvanted) Injectable Suspension - formerly Novavax COVID-19 Vaccine	Novavax, Inc.	Nuvaxovid (COVID-19 Vaccine, Adjuvanted) is a protein-based, non-MRNA vaccine for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	May 16, 2025
12.	Plaque Psoriasis, Psoriatic Arthritis, Crohn's Disease, Ulcerative Colitis	Starjemza (Ustekinumab -hmny) Injection	Bio-Thera Solutions, Ltd.	Starjemza (Ustekinumab-hmny) is a human interleukin-12 and -23 antagonist interchangeable biosimilar to Stelara used for the treatment of plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.	May 22, 2025
13.	Pulmonary Arterial Hypertension; Pulmonary Hypertension Associated with Interstitial Lung Disease	Yutrepia (Treprostinil) Inhalation Powder - formerly LIQ861	Liquidia Technologies, Inc.	Yutrepia (Treprostinil) is an inhaled dry powder formulation of the prostacyclin mimetic Treprostinil approved for the treatment of pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD).	May 23, 2025

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
14.	Adrenocortical Insufficiency	Khindivi (Hydrocortisone) Oral Solution - formerly ET-400	Eton Pharma-ceuticals, Inc.	Khindivi (Hydrocortisone) is an oral solution formulation of the approved corticosteroid hydrocortisone indicated as replacement therapy in paediatric patients 5 years of age and older with adrenocortical insufficiency.	May 28, 2025
15.	Dry Eye Disease	Tryptyr (Acoltremon) Ophthalmic Solution	Alcon Inc.	Tryptyr (Acoltremon) ophthalmic solution is a first-in-class TRPM8 thermoreceptor agonist indicated for the treatment of the signs and symptoms of dry eye disease.	May 28, 2025
16.	COVID-19	mNEXSPIKE (COVID-19 Vaccine, mRNA) Injection	Moderna, Inc.	mNEXSPIKE (COVID-19 Vaccine, mRNA) is a vaccine indicated for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).	May 30, 2025
17.	High Blood Pressure	Widaplik (Amlodipine, Indapamide and Telmisartan) Tablets – formerly GMRx2	George Medicines	Widaplik (Amlodipine, Indapamide and Telmisartan) is a single pill, triple combination therapy for the treatment of hypertension, including initiation of treatment.	June 5, 2025
18.	Pain	Xifyrm (Meloxicam) Injection	Azurity Pharma-ceuticals, Inc.	Xifyrm (Meloxicam) Injection is a non-steroidal anti-inflammatory drug (NSAID) for use in the management of moderate-to-severe pain in adults.	June 5, 2025

Continued ...

S. No.	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
19.	Merck	Enflonsia (Clesrovimab -cfor) Injection	RSV Vaccination and Immunization	Enflonsia (Clesrovimab-cfor) is a respiratory syncytial virus (RSV) F protein-directed fusion inhibitor indicated for passive immunization for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.	June 9, 2025
20.	Non-small Cell Lung Cancer	Ibtrozi (Taletrectinib) Capsules	Nuvation Bio Inc.	Ibtrozi (Taletrectinib) is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer.	June 11, 2025
21.	Bladder Cancer	Zusduri (Mitomycin) for Intravesical Solution - formerly UGN-102	UroGen Pharma Ltd.	Zusduri (Mitomycin) is a sustained release, hydrogel-based formulation of mitomycin for intravesical treatment of recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC).	June 12, 2025
22.	Hereditary Angioedema	Andembry (Garadacimab -gxii) Injection	CSL Behring GmbH	Andembry (Garadacimab-gxii) is an activated Factor XII (FXIIa) inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema in adult and paediatric patients aged 12 years and older.	June 16, 2025

Continued ...

S. No	Treatment Indication	Drug's Name	Company	Description	Date of FDA Approval
23.	ADHD, Binge Eating Disorder	Arynta (Lisdexamfetamine dimesylate) Oral Solution	Azurity Pharmaceuticals, Inc.	Arynta (Lisdexamfetamine dimesylate) is an oral solution formulation of the approved central nervous system (CNS) stimulant Lisdexamfetamine for use in the treatment of ADHD and binge eating disorder.	June 16, 2025
24.	Pre-Exposure Prophylaxis of HIV	Yeztugo (Lenacapavir) Tablets and Injection	Gilead Sciences, Inc.	Yeztugo (Lenacapavir) is a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1. FDA approved Yeztugo (Lenacapavir) as the First and Only HIV Prevention Option Offering 6 Months of Protection	June 18, 2025
24.	Alkaptonuria	Harliku (Nitisinone) Tablets	Cycle Pharmaceuticals	Harliku (Nitisinone) is a hydroxyphenyl-pyruvate dioxygenase inhibitor indicated for the reduction of urine homogentisic acid in adult patients with alkaptonuria.	June 19, 2025

(Ravindra Bangar)
Editor

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PURPOSE OF PEER REVIEW

It is widely accepted that Peer Review is the most valid form of research evaluation and it is a cornerstone in the process of bringing academic research to publication in the following ways:

Evaluation - Peer review is an effective form of research evaluation to help select the highest quality articles for publication.

Integrity - Peer review ensures the integrity of the publishing process and the scholarly record. Reviewers are independent of journal publications and the research being conducted.

Quality - The filtering process and revision advice improve the quality of the final research article as well as offering the author new insights into their research methods and the results that they have compiled. Peer review gives authors access to the opinions of experts in the field who can provide support and insight.

TYPE OF PEER REVIEW OF JOURNAL

Double blind peer review - names are hidden from both reviewers and the authors.

HOW TO REVIEW ARTICLES

Referees are sent invitations to review papers by journal editors. These requests are made via email. If you are asked to provide a review, in order to avoid delays, we would be grateful if you could let us know as soon as possible if you are unable to complete it at the time or if a problem arises after the invitation has been accepted. Suggestions for alternative reviewers are always gratefully received.

Below we present some advice and guidance about how to conduct a review and put together a reviewer report that will be effective and beneficial to authors:

ETIQUETTE

Timeliness - We understand that our reviewers are busy so it won 't always be possible for invitations to be accepted. Please let us know as soon as possible if you need to refuse a review or if a problem arises after the invitation has been accepted. We as editors are grateful to receive suggestions about someone else that might be suitable to do the review if you have to decline the invitation.

Conflict of Interest - It is important to highlight to us any conflict of interest that you feel might occur. If you review the paper, please do so as discretely and as quickly as possible.

Discussion - It is important to discuss with us any concerns that you have about the paper or any specific requirements for review if you are being invited to review for the first time. As editors are we open to discuss your expectations and journal requirements.

INDIVIDUAL JOURNAL REVIEWER GUIDELINES

These guidelines include a list of questions and will usually offer the reviewer the chance to make general comments

- Read the paper very carefully.
- Relevance to the publication.
- Significance of the research within the field.
- Originality of the work conducted. It is also important to consider whether the author has ever published a substantially similar paper elsewhere (if you suspect the work may not be original, please view our ethics page for information about how to deal with a variety of situations).
- The methodology employed during the research.
- Technical accuracy.

STRUCTURE AND COMMUNICATION

- Accuracy of references
- Overall Structure of the paper, communication of main points and flow of argument
- Quality of written language and structure of the article
- Effectiveness of the article abstract and introduction (some journals will request
- Whether the argument is clear and logical and the conclusions presented are supported by the results or evidence presented
- Whether the title of the article is suitable or effective
- Whether the abstract is a good summary of the article
- Whether the work meets with the article types accepted by the journal

The accessibility of the paper to a broad readership

Whether the paper is internally consistent

FEEDBACK IN YOUR REVIEWER REPORT - GIVING ADVICE TO AUTHORS AND SUGGESTING REVISIONS

- Be as objective as possible in your comments and criticisms and avoid making negative comments about work referenced in the article

- Be specific and as constructive as possible in your criticism. Be clear about what needs to be added or revised.
- If relevant, make suggestions about additional literature that the author might read to enrich or improve their arguments
- You should ensure that you are clear which of your comments you are happy for the author to see and which are meant specifically for the journal editor in order to avoid confusion or bad feeling
- While peer reviewers should feel free to make general comments on written quality and make suggestions about how articles might be improved by broadening reading of other literature, it is not the job of the peer reviewer to rewrite articles or suggest detailed changes to wording

MAKING A DECISION

> Recommend whether a paper should be accepted, rejected or revised (major or minor revisions)

> Most importantly, keep all activity, content and comments relating to the paper confidential

Publication Ethics and Publication Malpractice Statement

Our publication ethics and publication malpractice statement is mainly based on the Code of Conduct and Best-Practice Guidelines for Journal Editors (Committee on Publication Ethics, 2011).

EDITORS' RESPONSIBILITIES

Publication Decisions

The editor is responsible for deciding which of the papers submitted to the journal will be published. The editor will evaluate manuscripts without regard to the authors' race, gender, sexual orientation, religious belief, ethnic origin, citizenship, or political philosophy. The decision will be based on the paper's importance, originality and clarity, and the study's validity and its relevance to the journal's scope. Current legal requirements regarding libel, copyright infringement, and plagiarism should also beconsidered.

Confidentiality

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Disclosure and Conflicts of Interest

Unpublished materials disclosed in a submitted paper will not be used by the editor or the members of the editorial board for their own research purposes without the author's explicit written consent.

REVIEWERS' RESPONSIBILITIES

Contribution to Editorial Decisions

The peer-reviewing process assists the editor and the editorial board in making editorial decisions and may also serve the author in improving the paper.

Promptness

Any selected referee who feels unqualified to review the research reported in manuscript or knows that its prompt review will be impossible should notify the editor and withdraw from the review process.

Confidentiality

Any manuscripts received for review must be treated as confidential documents. They must not be disclosed to or discussed with others except as authorized by the editor.

Standards of Objectivity

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

Disclosure and Conflict of Interest

Privileged information or ideas obtained through peer review must be kept confidential and not used for personal advantage. Reviewers should not consider manuscripts in which they have conflicts of interest resulting from competitive, collaborative, or other relationships or connections with any of the authors, companies, or institutions associated with the papers.

AUTHORS' DUTIES

Reporting Standards

Authors of original research reports should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable.

Originality, Plagiarism and Acknowledgement of Sources

Authors will submit only entirely original works, and will appropriately cite or quote the work and/or words of others. Publications that have been influential in determining the nature of the reported work should also be cited.

Multiple, Redundant or Concurrent Publication

In general, papers describing essentially the same research should not be published in more than one journal. Submitting the same paper to more than one journal constitutes unethical publishing behavior and is unacceptable. Manuscripts which have been published as copyrighted material elsewhere cannot be submitted. In addition, manuscripts under review by the journal should not be resubmitted to copyrighted publications. However, by submitting a manuscript, the author(s) retain the rights to the published material.

Authorship of the Paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. The corresponding author ensures that all contributing co-authors and no uninvolved persons are included in the author list. The corresponding author will also verify that all co-authors have approved the final version of the paper and have agreed to its submission for publication. Disclosure and conflicts of interest

All authors should include a statement disclosing any financial or other substantive conflicts of interest that may be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and to cooperate with the editor to retract or correct the paper in form of an erratum.

Disclaimer

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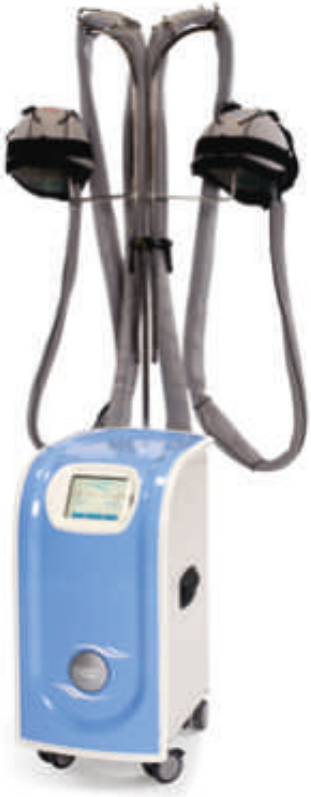
DEPARTMENT OF ONCOLOGY

SCALP COOLING MACHINE



Rajasthan's First Scalp Cooling Machine has been established in Pacific Medical College and Hospital, Udaipur for providing US FDA Approved Scalp Cooling Therapy to Cancer Patients to prevent hair-loss due to Chemotherapy.

PACIFIC IVF CENTER

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