SANKALCHAND PATEL UNIVERSITY
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Inaugural Message

It is with immense pride and joy that I present my heartfelt congratulations on the launch of the inaugural issue of the *Journal of Integrative Health Research (JIHR)*. This remarkable initiative exemplifies Sankalchand Patel University's unwavering commitment to advancing innovation and excellence in healthcare research while fostering the principles of integrative health.

In today's world, where healthcare faces growing complexities like chronic diseases and lifestyle disorders, integrative medicine offers a holistic and promising path. By combining the strengths of traditional systems of medicine with modern science, JIHR aims to create a platform for interdisciplinary research and collaboration that promotes better healthcare outcomes and patient-centric solutions.

I extend my heartfelt congratulations to **Dr. J. R. Patel, Director of Medical Sciences**, and **Dr. Vivekanand Kattimani, Editor-in-Chief of JIHR**, for their visionary leadership and tireless efforts in making this journal a reality. Their dedication to fostering excellence in research and creating a platform for global collaboration will undoubtedly make JIHR a cornerstone of integrative healthcare research.

The *Journal of Integrative Health Research* aspires to be a global platform for promoting evidence-based studies, clinical insights, and innovative approaches that integrate traditional and modern medicine. This journal reflects our shared vision of fostering interdisciplinary collaboration to address pressing healthcare challenges and improve lives.

As we celebrate this significant milestone, I invite researchers, academicians, and healthcare professionals worldwide to contribute to JIHR and join us in this transformative journey. Together, we can advance healthcare research and create a positive impact on global well-being.

With best wishes for the continued success of JIHR, let this inaugural issue mark the beginning of a legacy that inspires innovation and excellence in healthcare.

Shri Prakashbhai Patel
President
Sankalchand Patel University
Visnagar, Gujarat, India

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Inaugural Message

It is with immense pride and heartfelt joy that I write this inaugural message for the *Journal of Integrative Health Research (JIHR)*, a flagship initiative of Sankalchand Patel University. This journal represents a significant milestone in our ongoing pursuit of excellence in healthcare education, research, and practice.

The field of integrative health is witnessing a remarkable evolution as it brings together the time-honored traditions of holistic healing with the rigor of modern scientific research. At Sankalchand Patel University, we have always embraced the philosophy of blending the wisdom of the past with the innovations of the present. The launch of JIHR is a testament to this vision and reflects our unwavering commitment to fostering interdisciplinary collaboration in healthcare for the betterment of society.

I take this opportunity to extend my warmest congratulations to **Dr. J. R. Patel, Director of Medical Sciences**, for his unwavering dedication and dynamic leadership in bringing this initiative to fruition. His vision of creating a platform to promote high-quality research in integrative healthcare has been instrumental in the establishment of JIHR.

A special acknowledgment and heartfelt congratulations are also due to **Dr. Vivekanand Kattimani, the Editor-in-Chief of JIHR**, for his exemplary leadership of the editorial team and expertise, tireless efforts, and commitment to upholding the highest standards of scientific rigor and ethical integrity have been pivotal in shaping the journal into a credible and impactful platform for research dissemination.

The *Journal of Integrative Health Research* is poised to serve as a bridge between conventional and alternative medicine, creating a space for evidence-based studies, critical reviews, clinical insights, and innovative ideas. By embracing a holistic approach, the journal aims to contribute significantly to addressing the multifaceted healthcare challenges of the modern era, including the rise of chronic diseases, lifestyle disorders, and the need for patient-centered care.

As we celebrate this historic milestone, I invite researchers, academicians, clinicians, and policymakers from across the globe to join us in this transformative journey. Your contributions will be invaluable in building a robust body of knowledge that has the potential to redefine healthcare practices and improve lives.

Let us work together to make the *Journal of Integrative Health Research* a beacon of innovation, collaboration, and excellence in the healthcare community. I am confident that this initiative will leave a lasting impact on the future of healthcare and inspire new paradigms in integrative health research.

With best wishes for the success of JIHR and gratitude to all who have made this dream a reality, let us embark on this exciting journey to advance the frontiers of healthcare research.

Prof. (Dr.) Prafulkumar Udani
Honourable Provost
Sankalchand Patel University
Visnagar, Gujarat, India

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Inaugural Message

It is with immense pride and great pleasure that I present this inaugural message for the *Journal of Integrative Health Research (JIHR)*. This journal marks a significant milestone in the journey toward advancing interdisciplinary collaboration and promoting a holistic approach to healthcare.

The modern healthcare landscape calls for a convergence of traditional and contemporary medical practices to address the growing complexities of human health. The *Journal of Integrative Health Research* serves as a dedicated platform to bridge this gap, fostering dialogue between conventional medicine and alternative therapies such as Ayurveda, Yoga, and other traditional systems of healing. Our mission is to inspire evidence-based studies that enhance healthcare practices by combining innovation with the wisdom of age-old traditions.

I would like to take this opportunity to recognize and congratulate the efforts of the editorial team, led by **Dr. Vivekanand Kattimani, Editor-in-Chief of JIHR**. Under his visionary leadership, the team has worked tirelessly to bring this journal to fruition. Their dedication to ensuring scientific rigor, upholding ethical standards, and curating impactful research is commendable.

JIHR is committed to publish high-quality original research, review articles, clinical studies, and case reports that explore integrative health approaches. By fostering global collaboration, we aim to inspire innovative ideas and evidence-based solutions that address pressing healthcare challenges such as chronic diseases, lifestyle disorders, and rising healthcare costs.

I extend my gratitude to the editorial board, reviewers, and contributors for their relentless efforts in launching this journal. Your passion and commitment have laid a strong foundation for its success.

As we embark on this journey, I invite researchers, clinicians, and academicians worldwide to contribute their insights and discoveries to JIHR. Together, we can advance the frontiers of integrative healthcare, creating a positive impact on the well-being of individuals and communities.

With best wishes for the success of JIHR, let us move forward, united in our mission to revolutionize healthcare through integration, innovation, and collaboration.

Dr. J. R. Patel
Director, Health Sciences
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Editorial Message

With immense pride and enthusiasm, I present the inaugural issue of the *Journal of Integrative Health Research (JIHR)*, the official publication of the Sankalchand Patel University, Visnagar, Gujarat. This journal serves as a platform dedicated to integrating modern medicine and Indian systems of medicine, including Ayurveda, Homeopathy, Unani, and other traditional practices, reflecting the university's commitment to advancing interdisciplinary healthcare research.

The launch of *JIHR* comes as healthcare systems worldwide is evolving to embrace a more comprehensive, patient-centered approach. The integrative health model combines the strengths of modern medical advances with the time-tested wisdom of Indian traditional medicine. This approach not only promotes healing, but also emphasizes preventive care, wellness, and holistic treatment, offering a broader spectrum of care that meets the complex needs of patients today.

Bridging Modern and Traditional Medicine

At its core, integrative health acknowledges that modern medicine excels in diagnosing and treating acute and critical conditions through technological advancements, while Indian systems of medicine offer invaluable insights into chronic disease management, preventive care, and the promotion of overall well-being. The *JIHR* aims to bridge these two systems, encouraging dialogue, collaboration, and research that demonstrate the potential of combined approaches to healthcare.

Our vision for *JIHR* is to become a leading platform for sharing original research, reviews, clinical studies, and case reports that explore the integration of modern and traditional health practices. By fostering interdisciplinary research, we aim to advance knowledge that contributes to better health outcomes and improved patient care.

The Importance of Integrative Research

Integrative healthcare is gaining recognition not only in India but around the world. The increasing prevalence of chronic diseases, lifestyle-related health issues, and the growing demand for holistic, patient-centered care make it essential to explore all available medical systems. The combination of modern diagnostics and treatment strategies with the preventive and holistic approaches of Indian medicine systems can offer a more balanced and effective healthcare model.

At *JIHR*, we are committed to publishing high-quality, evidence-based research that highlights the benefits of such an integrative approach. Our goal is to ensure that both healthcare practitioners and researchers have access to innovative insights that promote interdisciplinary understanding and collaborative practice.

A Future of Collaboration

The establishment of *JIHR* is a testament to the vision of Sankalchand Patel University to promote integrative health research. I would like to extend my sincere gratitude to The Provost of the university and the editorial board for their dedication and support in making this journal a reality.

As we embark on this new journey, I invite researchers, clinicians, and healthcare professionals from all streams to contribute their work to *JIHR*. Together, we can shape the future of healthcare by integrating the best of modern and traditional medicine.

Warm regards,

Dr. Vivekanand Kattimani, MDS, Ph.D
Editor-in-Chief, Journal of Integrative Health Research
Head, Department of Clinical Research, Sibar Institute of Dental Sciences, Guntur.
Andhra Pradesh, India.

Efficacy of Low-Level Laser Therapy and Temporo-mandibular Joint Mobilization in subjects with Myo-facial Pain Syndrome

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Abstract

Background: Myo-facial Pain Syndrome (MPS) is a regional pain disorder that affects every age-group and is characterized by the presence of trigger points (TrPs) within muscles or fascia. When manual pressure is applied over an MPS, it produces a distinct local and referred pain that is consistent with the patient's presenting pain symptoms. There are various physiotherapy treatments available for MPS.
Objectives: As such there are controversial results regarding the therapeutic efficacy of Low-level laser therapy (LLLT) and Temporo-mandibular mobilisation in the management of MPS which has been demonstrated by previous studies. Additionally, there is no comparison between LLLT and Temporo-mandibular mobilisation for the treatment of MPS. The aim of the study was to find out the Efficacy of LLLT and Temporo-mandibular Joint Mobilization for the treatment of MPS.
Results: We found that both the techniques are useful to decrease pain intensity and improvement in maximum mouth opening in subjects with MPS.
Conclusion: Physical therapy interventions, TMJ joint mobilization and LLLT showed significant clinical improvement in reduction of pain and maximal mouth opening of the individuals with MPS. There was no statistical difference seen between the treatment modalities.
Keywords: Myo-facial pain syndrome (MPS), low level laser therapy (LLLT), Temporo-mandibular (TMJ) mobilization.

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Introduction

Myo-facial Pain Syndrome (MPS) is a regional pain disorder that affects every age group and is characterized by the presence of trigger points (TrPs) within muscles or fascia.[1] Commonly recognized as "muscle knots," MPS is the most common cause of persistent regional pain. Simon's original definition of MPS is defined as a "complex of sensory, motor, and autonomic symptoms that are caused by Myo-facial trigger points". [1]

When manual pressure is applied over an MPS, it produces a distinct local and referred pain that is consistent with the patient's presenting pain symptoms.[2] MPS is often grouped with other pain syndromes**;** however, it is distinct from

diagnoses such as fibromyalgia in that it is focal, does not require multiple pain generators, and involves a taut band in skeletal muscle.

The exact prevalence of MPS in the general population is infrequently cited in existing literature, some studies have estimated that MPS comprises 30 - 85% of cases of musculoskeletal pain.[1] The people most affected by this condition are between the ages of 27- 50 years.[1] Any difference between genders has not yet been determined. Although the patho-physiology of MPS is still not well understood, it is thought to be due to muscle overload as a result of either overuse or disuse.[1]

There have been several risk factors identified that contribute to the development of MPS which include traumatic events, ergonomic factors (e.g., poor/ abnormal posture, overuse activities, etc.), structural factors (e.g., osteoarthritis, scoliosis, etc.) and systemic factors such as hypothyroidism, vitamin D deficiency, and iron deficiency.[2]

Despite the prevalence of MPS, its patho-physiology remains incompletely under-stood. One hypothesis suggested that TrPs are due to a dysfunction of the neuromuscular junction and surrounding connective tissue. Electromyography studies have revealed some evidence of abnormal electrical activity at the motor endplates of neurons terminating on muscle fibers of a TrP. Excessive electrical activity was identified as excess acetylcholine (ACh) release,[3] both of which propose possible mechanisms for the formation of TrPs and the development of MPS.

Among different physiotherapeutic methods for the treatment of MPDS, LLLT has gained popularity due to its conservativeness. LLLT has shown analgesic, healing, and anti-inflammatory effects on irradiated tissues. Temporo-mandibular mobilization is an additional treatment modality for MPS. This active-assistive technique is performed in order to increase opening by theoretically taking advantage of reciprocal inhibition. [4]

Materials and Method

Forty MPS patients with limited mouth opening were selected from the Orthopedic Physiotherapy OPD of Nootan College of Physiotherapy. Limited mouth opening was defined as pain-free unassisted mandibular opening of <40 mm.[7] Subjects who received analgesic or antidepressant medicine or underwent any other form of treatment for Temporo-mandibular joint disorder were excluded from the study. The study was approved by the ethics committee of Nootan College of Physiotherapy, Sankalchand University. The purpose of the study was described to each participant and an informed consent was obtained prior to the start of treatment. The cases were randomly divided into LLLT and TMJ mobilisation groups with 20 patients in each group.

Laser calibration was done before use and the laser probe was disinfected with an alcohol swab before each treatment. The laser device was a gallium-aluminum-arsenide diode source (Doctor Smile Diode Laser, Italy) with a wavelength of 810 nm and a continuous 0.5 W peak power output beam with 5 mm spot size. The probe was held perpendicular with a light pressure on the targeted muscle. The masticatory muscles were evaluated bilaterally with firm and constant pressure to define painful areas. Laser group patients received 12 sessions of LLLT (Table 1).

Table 1: LLLT irradiation protocol

Day	1st week	2nd week	3rd week	4th week
Saturday	0.5 W	0.2 W	0.3 W	0.1 W
Sunday	0.4 W			
Monday	0.3 W	0.3 W		
Tuesday	0.2 W			
Wednesday	0.1 W	0.4 W	0.2 W	0.2 W

For group 2 TMJ mobilization treatment were given in two techniques. The first is a passive technique called "long-axis distraction." In this technique, the therapist places his or her thumb on the patient's lower posterior molars and the index or middle fingers under the distal chin. The head is stabilized by the chest and opposite hand. By gently pressing inferiorly with the thumb and stabdizing the distal chin, the therapist can distract the mandible along the long axis of the condyle. We believe this technique should be administered gently and held for approximately 5 seconds, then repeated three to five times or as needed (Fig 1).

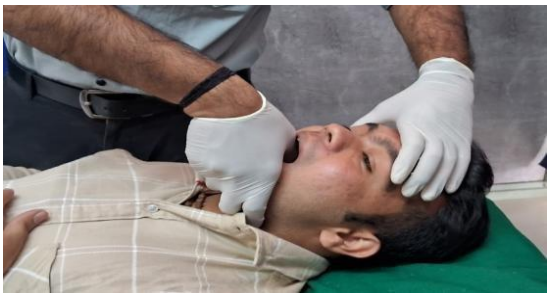

Fig 1: Mobilization technique for the long-axis distraction of temporomandibular joint.

Fig 2 Low level LASER Therapy

The second mobilization technique was "overpressure with an opening." This technique involves the same hand placement and stabilization as used for long-axis distraction. The patient was asked to open mouth as wide as possible. The therapist then gently presses down on the molars. This produces an "overpressure" with an opening. It is held for about 5 to 10 seconds and repeated three times. The treatment was given for 5 days/week for 4 weeks. Pre and post treatment maximum mouth opening and pain scale were recorded.

Results

All participants completed the study period. Thirty patients (75%) were female and 10 (25%) were male. In this study, the mean age of subjects was 36±12.34. (Table 2)

Discussion

LLLT and TMJ mobilisation is a non-invasive, rapid, safe and non-pharmaceutical treatment method that may be beneficial for patients with MPD. Thus the aim of this study was to evaluate whether LLLT or TMJ mobilisation could reduce pain intensity and improve mouth opening in patients with MPDS.

As per the results, 95.86% pain reduction occurred in both group, while the pain did not recur in the follow-up period. The mechanisms of action behind the therapeutic and analgesic effects are variable and include the release of endogenous opioids, enhancement of cellular respiration and tissue healing, vasodilation, increased pain threshold by changing the action potential of cell membranes, and decreasing inflammation by reducing prostaglandin E2 and cyclooxygenase 2 level.[5] Emshoff et al (632.8 nm, 30 mW, 1.5 J/cm^2), Carrasco et al (780 nm, 50/60/70 J/cm2) and da Cunha et al (830 nm, 500 Mw, 100 J/cm^2), who reported a significant reduction of pain intensity in both laser and placebo groups, suggesting that improvement was mostly due to the placebo effect of laser administration. Similar to the results of our study Marini et al also postulated that pain severity and mandibular function improved in all patients who received LLLT and it has been more efficient in the treatment of pain caused by TMJ disorder compared to ibuprofen.[6]

Table 2: Result of both groups from 1 - 4 weeks.

Mean	1st week	2nd week	3rd week	4th week
Changes in Mean Subjective VAS in Groups in the Whole Treatment Phase	7.25±1.51	5.65±1.69	4.80±1.79	2.75±2.19
Changes in mean subjective Maximum Painless Mouth Opening During the Treatment	31.63±7.35	33.05±5.94	33.94±5.63	39.00±8.84

In this research a significant improvement was observed in maximum painless mouth opening in both group. Results demonstrate 33.60% increase in mouth opening in both group which started from the first session. It means that LLLT shows the functional improvement and the objective functional parameters for the patients occurred later than the decrease in pain intensity which coordinates with literature.[7,8,9] TMJ mobilization techniques showed that the motor neurons to the antagonists to jaw opening (masseter, temporalis, and medial pterygoid muscles) should be inhibited as the patient uses the agonists (lateral pterygoid, suprahyoid, and infrahyoid muscles) to volitionally open the mouth wide. This technique should facilitate a decrease in muscle guarding.[6,10]

Conclusion

This study concluded that both physical therapy interventions i.e. TMJ joint mobilization and LLLT showed significant clinical improvement in reduction of pain and Maximal mouth opening of the individuals affected by MPS.

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Conflict of Interest: None declared

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Evaluate the effectiveness of cryotherapy on reduction of pain during arterio-venous fistula puncturing among patients undergoing hemodialysis at Amaravathi Hospital, Karur (Dt), Tamil Nadu.

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Abstract:

Introduction: The aim of the study was to evaluate the effectiveness of cryotherapy on reduction of pain during arterio-venous fistula puncturing among patients undergoing hemodialysis.
Materials and Method: 60 samples were selected including 30 samples in the Experimental group and 30 samples in control group. The data was collected by using Numerical Pain Rating Scale. For Experimental group cryotherapy was administered. In the control group, the post test was conducted without intervention. Each day 5 – 10 hemodialysis patients are assessed during the data collection period. The data was analyzed by using descriptive and inferential statistics.
Results: There was a significant difference between experimental group and control group after administering cryotherapy. The pain level was reduced. Chi square analysis was done to associate post test score with selected demographic variables. There is a significant association between the post test score and demographic variables in the experimental group.
Conclusion: Cryotherapy is highly effective in reducing arterio venous fistula puncturing pain among hemodialysis patients.
Keywords: Arterio-venous fistula puncture, hemodialysis, cryotherapy

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Introduction

Chronic Kidney Disease is a Global health crisis. Chronic kidney disease burden is increasing worldwide. In the 2015 global burden of disease study shows kidney disease was the 12th most common cause of death accounting for 1.1 million deaths worldwide. Overall CKD mortality has increased by 31.7% over the last 10 years making it one of the fastest rising major causes of death.1,2

About 1,75,000 new people have kidney failure every year in India and require dialysis. Pain during arteriovenous fistula cannulation remains a common problem among hemodialysis patients that leads to noncompliance to lifetime maintenance of haemodialysis.3 Arterio-Venous Fistula puncture causes pain even though local anesthesia is not frequently used due to concerns of vasoconstriction, burning sensation, scaring and infection. The

frequent pain induced by fistula puncture can result in depression, avoidance or shortening of session duration. Cryotherapy is the application of cold material that removes heat from the body resulting in decreased tissue temperature. It decreases tissue blood flow by causing vasoconstriction and reduces tissue metabolism and muscle spasm. These result in a local anesthetic effect called cold-induced neuropraxia.4,5

Objectives:

1. To compare the effectiveness of Cryotherapy on reduction of arteriovenous fistula puncture pain among experimental and control group of patients undergoing hemodialysis
2. To find the association between the posttest arteriovenous fistula puncture pain level among patients undergoing hemodialysis with their selected demographic variables.

Hypotheses:

H1: There is a significant difference between arteriovenous fistula puncture pain level among patients undergoing hemodialysis in experimental and control group.
H2: There is a significant association between arteriovenous fistula puncture pain level and their selected demographic variables of patients undergoing hemodialysis.

Materials and Method

The research approach adapted was an evaluative approach. The research design is one group posttest only design. This study was conducted in Amaravati hospital, Karur Tamil Nadu. The chronic renal failure patients undergoing hemodialysis are the population.

The researcher obtained formal permission to conduct the study from the Principal of Sri Aurobindo College of Nursing, Ethical Committee, and the Director of Amaravati hospital, Karur. 60 samples were selected by using convenience sampling technique. 30 samples were allotted for the experimental group and the remaining 30 for control group. Both males and females are included. The age group is between 18 to 70 years and the patient those are having cardiovascular disease, Raynaud's disease, peripheral vascular disease are excluded.

The cryotherapy was administered for experimental group. Filled the glove with ice cubes and started giving ice massage at the web between the thumb and index finger for 10 minutes before puncture and continued 2 minutes after the puncturing procedure. The post test was conducted after 2 minutes. It continued for 1 month. In control group without administering the intervention the post test was conducted after 2 minutes of arterio-venous fistula puncture procedure for 1 month and compared the effectiveness of intervention. Each day around 5 – 10 hemodialysis patients are assessed

Materials:

Tool consists of three sections.
Section A - Demographic variables,
Section B - clinical variables,
Section C - numerical pain rating scale.

Results

After administration of cryotherapy among experimental group majority 16 (53.33%) of had mild pain, 14 (46.67%) of them had moderate pain. (Table 1) In the control group majority 24 (80%) of them had severe pain, 6 (20%) of them had moderate pain, and 0 had no pain. This revels there is a significant difference between experimental and control groups regarding arterio-venous fistula puncture pain score among hemodialysis patients (Table 2).

In experimental group, the posttest mean score is 3.37, SD 1.65, in control group the

Table 1: Shows the post-test Level of pain score among the Experimental and Control group

Level of pain	Group			
	Experimental Group (n=30)		Control Group (n=30)	
	F	%	F	%
No Pain	0	0.00	0	0.00
Mild Pain	16	53.33	0	0.00
Moderate Pain	14	46.67	6	20.00
Severe Pain	0	0.00	24	80.00

Table 2: Post-test Mean, SD, and 't' test score of Arterio-venous fistula puncture pain level among patients undergoing hemodialysis

Group				Mean difference	t-test	Table Value
Experimental (n=30)		Control (n=30)				
Mean	SD	Mean	SD			
3.37	1.65	7.93	1.34	4.56	t=11.77 p=0.001** * (S)	2.20

Table 3: Shows the association between post-test level of pain score with demographic variables of hemodialysis patients in the experimental group

Demographic variables	Level of pain score						n	Chi square test
	Mild		Moderate		Severe			
	F	%	F	%	F	%		
Age in years								2=8.92 P <0.05* (S)
a) 18 – 30 yrs	1	14.29	6	85.71	0	0.00	7	
b) 31– 45 yrs	2	33.33	4	66.67	0	0.00	6	
c) 46 – 60 yrs	6	75.00	2	25.00	0	0.00	8	
d) 61 – 70 yrs	7	77.78	2	22.22	0	0.00	9	
Gender								2=6.46 p>0.01** (S)
a) Male	12	66.67	4	33.33	0	0.00	16	
b) Female	4	28.57	10	71.43	0	0.00	14	
Site of AV Fistula								2=9.19 p<0.03* (S)
a) Radio-cephalic-AVF	4	100.00	0	0.00	0	0.00	4	
b) Brachio-cephalic-AVF	2	28.57	5	71.43	0	0.00	7	
c) Brachio-basilic-AVF	10	62.50	6	37.50	0	0.00	16	
d)Ulnar-basilic-AVF	0	0.00	3	100.00	0	0.00	3	

post-test mean score is 7.93, SD 1.34 and the mean difference is 4.56, the calculated 't' value is =11.77(p=0.001). The table 't' value is 2.20. It inferences that the calculated 't' value is higher than the table 't' value. It shows that cryotherapy is highly effective in reducing arteriovenous fistula puncture pain among hemodialysis patients. So, the research hypothesis H1 is ace Chi–square test was used to find out the association between the post test score of arteriovenous fistula puncture pain with demographic variables age, gender, education, occupation, place of living, marital status, family income, nutritional habits, bad habits, duration of disease, frequency of dialysis, presence of arteriovenous fistula in arm, co-morbidity illness, site of arteriovenous fistula, duration of present arterio-venous fistula.

out of which age (p=0.05) gender (p=0.01), site of arterio-venous fistula (p= 0.03) are significant with post test score. The rest of the demographic variables have no significant with post-test level of pain score in experimental group. In control group none of the demographic variables associate with posttest pain score. (Table 3)

Conclusion

Based on the results it is concluded that, cryotherapy was effective on decreasing pain intensity among patients undergoing hemodialysis at puncture sites of arteriovenous fistula. It can be used as a non-pharmacological intervention and is recommended as a pain-relief technique during AV fistula puncture in hemodialysis patients. Cryotherapy is a low-risk and uncomplicated method seems to be effective and useful in reducing pain.

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Aversive Conditioning: Hand-over-Mouth Technique & Physical Restraint

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Abstract

It is generally acknowledged that behaviour control is important in providing children with dental care. Indeed, it is challenging, if not impossible, to do any necessary dental care if a child's behaviour in the dental office is not controlled. Usually, various psychological behaviour management techniques are used in child in dental clinic. But when all psychological behaviour management techniques fail to calm down the child then use of physiological management techniques like Hand over Mouth Exercise & Physical Restraint are used to eliminate the inappropriate behaviour of child and deliver the dental treatment with the consent of parents.

Keywords: Hand-over-mouth technique, Physical restraint, Children, Pediatric Dentistry

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Introduction

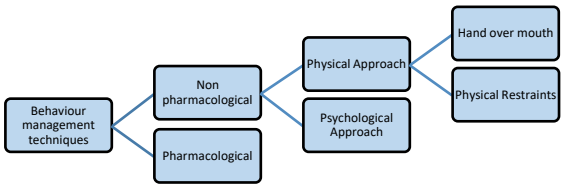
The American Academy of Pediatric Dentistry (AAPD) recognizes that dental care is medically necessary for the purpose of preventing and eliminating oro-facial disease, infection and pain, restoring the form and function of the dentition, and correcting facial disfiguration or dysfunction.[1] Behaviour is any activity that can be observed, recorded and measured.[2] A child's good behaviour is not magic; it takes various skills of encouragement to help them through their distress. One of the main qualities of a dentist is to manage a child positively while satisfying their dental needs. Thereby instilling a positive dental attitude and good oral health in them.[3] Wright et al. (1975) defined behaviour management as the method by which the dental health team treats a young patient effectively and efficiently while also fostering a healthy dental attitude.[2,3]

Objectives of behaviour management:[2]
According to Snowder (1980),

- To establish effective communication with child and parent
- Gain child and parent confidence for dental treatment
- Teach child positive aspect of preventive dental care
- Provide a comfortable, relaxing environment to the child

Classification of behavior management techniques:[2]

The first national clinical guidelines on non-pharmacological behaviour management techniques were published online by the Royal College of Surgeons (England) in 2002.[3,4]



Hand–over–Mouth Technique (Home):
This technique was first described in 1920 by Dr. Evangeline Jordan.
Dr. Evangeline Jordan wrote "if a normal child will not listen but continues to cry and struggle – hold a folded napkin over the child's mouth and gently but firmly hold the mouth shut. His scream increased his condition of Hysteria, but if the mouth is held closed, there is little sound, and he soon begins to reason".[2]
As described by Craig (1971) the purpose of the technique is to gain the attention of a child to allow communication.[5] Rombom et al (1981) argued that the technique is best described in psychological terms as response prevention, a flooding procedure, rather than an aversive technique.[6]

Barton (1993) suggested HOME might better be described in terms of negative reinforcement, where the child's behaviour of stopping the protest and being quiet is reinforced by the cessation of the unpleasantness of not being allowed to protest loudly and of having his/her limbs restrained. It has been found that children do not remember, nor are affected by, hand over mouth/restraint experiences.[7] Table 1 shows types of mechanical aids for protective stabilization.[1]

Other terminologies: Emotional surprise therapy by Lampshire, HOM Airway Restricted (HOMAR) by Levitas (1947), Aversion by Crammer (1973), Aversive Conditioning by Lenchner and Wright (1975)[2]

Objectives:
- To gain child's attention enabling communication with dentist so that appropriate behavioral expectation can be explained.
- To eliminate inappropriate avoidance behaviour to dental treatment and to establish appropriate learned response.
- To increase child's confidence in coping with anxiety provoking dental stimuli.
- To assure child safety in delivery of quality dental care.[2]

Indications:
- A healthy child who is able to understand and cooperate but who exhibits defiant, obstreperous or hysterical behaviour to dental treatment.[2]
- Mainly used in age-range 3-8 years old and with children who are capable of effective communication[8]

Contraindications:
- Immature child
- When it prevents child from breathing
- When the dentist is emotionally involved with the child[2]
- Any child whose mental capacity and command of language means that effective communication would be impossible[8]

Technique:
- When indicated, a hand is placed over child's mouth and behavioural expectations are calmly explained.
- Child is told that the hand will be removed as soon as the appropriate behaviour begins.
- When child responds, the hand is removed and child's appropriate behaviour is reinforced.
- If the child shows negative behaviour again the procedure is repeated[2]

Legality of use of home:

- It has been pointed out that the use of HOME will not subject the dentist to liability by the patient when it is used properly with parental consent.
- Use of Hand Over Mouth Airway Restricted (HOMAR) is more nearly objectionable legally and may result in liability of the dentist.[2]

Review of literature:

Association of Pedodontic Diplomates (1970) found out that 80% Pediatric Dentist used HOME technique frequently.[2]

Acs G et al (1990) suggested that HOM was indicated in situations other than for the control of hysterical and tantrum-like behaviour.[9]

Carr et al. (1999) found out the number of clinicians who did not practice HOME was around 57%.[10]

Adair et al. (2004) observed that 79% of the clinicians did not use HOME.[11]

Hassan SQ et al (2010) did the survey to check the alternative behaviour management techniques that might be utilized by pediatric dentists in place of HOME after its elimination from the clinical guidelines of the AAPD. He found that 50% pediatric dentist believed that HOME is an acceptable behaviour management technique, and 41% believed it should be continued to be recognized by the AAPD. Only 7% believed that HOME elimination affected access to care for some children.[12]

Desai SP et al (2019) conducted study to assess the attitudes of parents of children towards Behaviour management techniques used by pediatric dentists. He found tell show do, positive reinforcement, and live modeling were the most accepted techniques, while the least accepted techniques were HOME and voice control technique.[13]

Segarra Ortells C et al (2021) did the survey of members of the Spanish Society of Pediatric Dentistry about behaviour modification techniques and He found the most common techniques were Tell Show Do and positive reinforcement, while the most abandoned HOM because it was rejected by parents and because of potential legal problems and psychological consequences for the patients.[14]

Variations of the techniques: Airway uninstructed, hand over both nose and mouth (HOMAR), towel held over mouth only, dry towel over nose and mouth, wet towel over nose and mouth.[2]

Protective stabilizers: Partial or complete immobilization of the patient is sometimes a necessary and effective way to diagnose and deliver dental care to patients who need help in controlling their extremities. Immobilization is also useful for managing combative, resistant patients, so that the patient, practitioner or dental staff may be protected from injury while care is being provided. The parents must be informed and the consent must be documented, before immobilization is used, they should have a clear understanding of the type of immobilization to be used, the rationale, and duration of use.[2]

The AAPD Standard of Care for Behaviour Management, revised in May 1996, indicates that the need to diagnose and treat, as well as protect the safety of the patient and practitioner, must justify the use of immobilization. This decision should take into consideration the patient's emotional development, physical and medical considerations, dental need, other alternative behavioural modalities and the quality of dental care. The older terminology of physical restraints has been replaced with the term medical immobilization or protective stabilization because we are not just strapping the child to the chair minimizing his movement. The idea is to immobilize the child benefiting and protecting both the child and the dentist.[2]

Active immobilization involves restriction of movement by another person such as the parent, dentist, or dental auxiliary. Passive immobilization utilizes a restraining device.[11]According to Frankel et al (1991) Restraint in the dental setting is the act of physically limiting the body movements of the child in order to facilitate dental procedures and to decrease possible injuries to the child and/or dentist.[15]

Whole-body restraint is often used in conjunction with sedation for patients who have physical or mental handicapping conditions to help prevent involuntary limb or head movements or in very young children as an alternative to sedation or general anaesthesia.[8]

Objective:

- Used to control unwanted physical movement of the child, both to facilitate treatment and also to prevent harm to the child and dental staff.[8]
- Facilitate delivery of quality dental treatment.[16]

Indications:

- A patient who requires diagnosis or treatment and cannot cooperate because of lack of maturity.
- A patient who requires diagnosis or treatment and cannot cooperate because of mental or physical disabilities.
- A patient who requires diagnosis or treatment and does not cooperate after other behaviour management techniques have failed.
- When the safety of the patient or practitioner would be at risk without the protective use of immobilization.[2]
- To control involuntary movement with sedated patients,
- When sedation or general anaesthesia are not available or permitted by parents.[8]

Contraindications:

- A cooperative patient
- A patient who cannot be safely immobilized because of underlying medical or systemic conditions
- As punishment
- It should not be used solely for the convenience of the staff.[2]
- a patient with a history of physical or psychological trauma, including physical or sexual abuse or other trauma that would place the individual at greater psychological risk during restraint.[16]

Connicket al (2000) distilled 5 salient points on use of restraint:[17]

i. It should only be used when absolutely necessary
ii. The least restrictive alternative should be chosen
iii. It should not be used as punishment
iv. It should not be used solely for the convenience of the dental team
v. Staff should closely monitor its use.

Precautions:[18,19]

The following precautions are recommended:

The patient's medical history must be reviewed carefully to ascertain any medical conditions or medications that can compromise physiologic function, may contra indicate the use of protective stabilization, or are associated with specific risk factors including: Cardiac instability, Pulmonary and respiratory instability, Musculoskeletal alignment issues or weakness, Joint hypermobility, Bone fragility, Cutaneous vulnerability to mechanical stress, Psychological instability, Thermoregulation disorders, Psychotropic medications, Tightness and duration of the stabilization must be monitored and reassessed at regular intervals, Stabilization around extremities or the chest must not actively restrict circulation or respiration;

Observation of body language and pain assessment must be continuous to allow for procedural modifications at the first sign of

distress; and stabilization should be terminated as soon as possible in a patient who is experiencing severe stress or hysterics to prevent possible physical or psychological trauma.

Table 1: Types of mechanical aids for protective stabilization:[1]

PART	AID	FEATURES
Mouth	Tongue blades Open wide mouth prop	These can be used directly to open mouth It has a durable foam core on the outside of a tongue depressor It is also easy to use, durable and available in two sizes
	Molt mouth prop	It can be very helpful in the management of a difficult patient for a prolonged period. It is made in both adult and child sizes, allows accessibility to the opposite side of the mouth Its disadvantages include the possibility of lip and palatal lacerations and luxation of teeth if it is not used correctly The patient's mouth should not be forced beyond its natural limits because patient's discomfort and panic will result, causing further resistance and perhaps airway compromise
	Rubber bite blocks	Available in various sizes to fit on the occlusal surfaces of the teeth and stabilize the mouth in an open position. The bite blocks should have floss attached for easy retrieval if they become dislodged in the mouth
	Finger guards	Used directly to open mouth
Body	Papoose Board	Simple to store and use It is available in areas to hold both large and small children It has attached head stabilizers It is reusable Necessary to monitor respiration if it is used in combination with sedation An extremely resistant patient may develop hyperthermia if immobilized too long Any restrained patient requires constant attendance and supervision
	Triangular sheet	Mink described this technique using a triangular sheet to control an extremely resistant child It allows the patient to upright during radiographic examinations Its disadvantages include the frequent need for straps to maintain the patient's position in the chair, the difficulty of its use on small patients, and the possibility of airway impingement Hyperthermia may be another problem during long periods of immobilization The need for constant supervision is emphasized so that these problems may be avoided
	Pedi-Wrap	Comes in various sizes and allows some movement while still confining the patient Its mesh fabric prevents developing hyperthermia Requires straps to maintain body position in the dental chair Constant supervision to prevent the patient from rolling out of the chair
	Beanbag dental chair insert	Developed to help comfortably accommodate hypnotic and severely spastic persons who need more support and less immobilization in a dental environment It is reusable and washable, and one size fits most people Many patients with physical disabilities relax more in this setting
	Safety belt and extra assistant	Useful in controlling movements
Extremities	Posey straps Velcro straps Towel and tape Extra assistant	Fasten to the arms of the dental chair and allow limited movement frequently prevents overreaction by resistant or combative patients Helpful for an athetoid-spastic cerebral palsy patient who tries desperately, but without success, to control body movements
Head	Head positioner Plastic bowl Extra assistant	Used to stabilize head

Review of literature:

Association of Pedodontic Diplomats (1972) conducted a survey and found out that 84% of the pediatric dentist's used physical restraints in selected patients.[2]

Nathan JE (1989) observed that only 4% of the pediatric dentist's employed immobilization technique. [2]

Newton JT et al (2004) did the questionnaire survey of pediatric dentist and found a large proportion of practitioners (62%) felt that the use of physical restraint was appropriate with certain disabled patients. The most commonly anticipated psychological sequeala which may accompany the use of these techniques was subsequent fear of dental treatment.[3]

Boka V et al (2014) examine the acceptance by Greek parents of nine behaviour-management techniques and he found least accepted techniques were passive restraint and General Anaesthesia.[20]

Guinot F et al (2021) compare the acceptance of behaviour management techniques used in pediatric dentistry by Spanish and Portuguese parents. From the 8 different behaviour management techniques the least accepted techniques in both countries were active and passive restraint.[21]

Ramadevi RP (2024) did the study to elicit parents' opinion and record their response to their children's experience who underwent dental treatment with an extra assistant for protective stabilization. In result she found the dental assistant was most preferred as the extra assistant to provide active stabilization. An overwhelming 98% of the parents agreed to protective stabilization with an extra assistant as advantageous and a good 88% of the parents recommended its use for further appointments of their children.[22]

Conclusion

This literature review has described the various modalities available in a clinical scenario. However, it is pertinent to prioritize psychological approaches first. Avoid resorting to physiological methods for behaviour management unless absolutely necessary, as they can impact a child's long-term behaviour. Judicious use of physical restraints with parental consent would aid safe completion of treatment modalities while avoiding legal implications.

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Minimally Invasive Periodontal Therapy: A Paradigm shift

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Abstract

Periodontitis is a complex term that affects all supporting tissues of the teeth and can be treated non-surgically as well as surgically. Periodontal therapy success is contingent on adequate case selection, patient cooperation, accurate diagnosis, and treatment plan. From a clinical standpoint, improved visualization during periodontal operations is required to achieve better results. Minimally invasive periodontal therapy (MIPT) explains need of utilizing minimally invasive techniques and provides information on how to improve visualization using a minimally invasive approach. Also, the reasons for minimally invasive periodontal procedures as well as numerous strategies for minimally invasive nonsurgical and surgical periodontal procedures in this Review will be explored.
Keywords: Illumination**,** Microsurgery, Magnification, Periodontitis

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Introduction

For decades, the traditional non-surgical and surgical procedures for treating chronic periodontitis remained constant. We treat chronic periodontitis cases with these techniques by using all the blind non-surgical ways to rely on tactile perceptions to locate and remove subgingival deposits. For example, in nonsurgical periodontal therapy, root planing entails removing some structure of the teeth during periodontal instrumentation to obtain a 'hard' and 'smooth' root surface. Because it requires the removal of some tooth structure, it is an intrusive treatment. However, in early 1980s concluded that the purposeful removal of cementum during the technique of root planning was not justified[1,2] and therefore a new idea was established for the treatment of damaged teeth. There is evidence suggesting that extensive surgery may be necessary to address underlying bony defects in cases where the pockets are deeper.

Traditional surgical procedures for periodontal disease often involve creating a large flap to access the affected area, resulting in bone exposure. To address the shortcomings of traditional procedures, Minimally Invasive Surgery (MIS) was introduced in 1995 by Harrel and Ress.[3] MIS aims to minimize incisions and flap reflection, making it less time-consuming, less painful, more acceptable, beneficial, and cost-effective. This newer technique involves using micro incisions design to obtain all surgical therapies that were previously done through larger surgical access for the treatment of periodontal diseases. MIS allows for a gentler handling of both soft and hard tissues during surgery.

Objectives of Minimally Invasive Periodontal Therapy:[4]

- Minimum surgical trauma
- Increase stability of flap/wound
- Primary wound closure stability
- Less time on operating
- Reduce patient pain and discomfort while minimising side effects

Types and Principles of Magnification System:

Precision is essential to the art of dentistry, and while the naked eye can detect fine details, enhancing and enlarging images can yield even better results. Despite the interest in microsurgery among dental professionals, many lack the necessary skills to perform such procedures, indicating a lack of understanding of its potential.[5] Periodontal microsurgery entails utilising a microscope to improve visual acuity at magnifications greater than 10x, and the use of loupes, surgical operating microscopes, and micro tools has elevated periodontal surgery to a new level of precision.

Application of periodontal microsurgery in procedures such as periodontal flap and recession coverage, periodontal regeneration, and implant surgery. The microsurgical triad, consisting of magnification, illumination, and refined surgical skills, is essential to achieving improved accuracy in surgical interventions **(Belcher et al. 2001).**[6] without any one of these elements, microsurgery is not possible. Enhancing the micro-surgical triad through the use of surgical microscopes and micro instruments can refine basic surgical techniques and improve surgical outcomes.

Dentists now have access to a wide selection of basic and complex magnifying systems, allowing them to improve the precision of their clinical abilities.

There are two types of optical magnification available to dentists which includes, Surgical Loupes and Surgical Operating Microscope

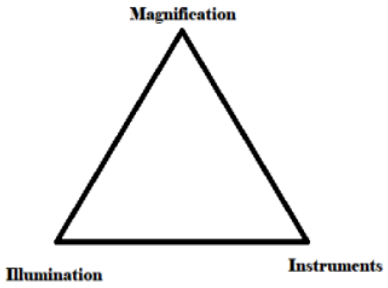

Fig.1 Magnification Triad

Surgical Loupes: Magnification loupes represent the most frequently employed magnification technique in the field of dentistry. These loupes consist of two separate monocular microscopes positioned next to each other to focus on a specific object. Dentistry commonly utilizes three distinct types of loupes, all employing convergent optics. These loupes are as follows: [7,8] Simple loupes, Compound loupes and Prism loupes

Surgical Operating Microscope: The Operational Microscope that enhanced adaptability and ease of use when compared to magnifying surgical loupes. However, comes with a significantly higher cost and a steeper learning curve initially. In the realm of dentistry, operational microscopes are designed based on Galilean principles. These scopes combine magnifying loupes with a magnification changer and a binocular viewing system, creating binoculars that work in parallel to minimize eye strain and fatigue. With fully coated optics and achromatic lenses, operational microscopes deliver higher quality of resolution and high colour contrast stereoscopic vision.

Working of Surgical Microscope:

To appreciate the working of surgical operating microscope one needs to have knowledge about the following.[9] Magnification, Illumination, Documentation, Accessories.

Effective microsurgical procedures demand precise instruments. A typical toolkit comprises all types of micro surgical instruments. In the field of Periodontics, various ophthalmic knives, such as the crescent, lamellar, blade breaker, sclera, and spoon knife, find application. Their distinct advantage lies in their exceptional micro sharpening ability and diminutive size. This combination reduces tissue trauma and expedites the healing process. Notably, these sharp instruments are etched rather than conventionally honed, ensuring a more precise wound edge.[10]

Instruments for Periodontal Microsurgery[11]

In the field of Periodontology, a variety of ophthalmic knives, including the curved shaped, lamellar, blade breaker, sclera, and spoon knife. Ophthalmic knives have the advantage of being both extremely sharp and small in size. This reduces tissue stress and speeds up healing. Ophthalmic knives' sharper blades generate a more precise wound edge because they are chemically etched rather than honed. The reduced size of the ophthalmic blades, when compared to the normal No.15 blade typically used in Periodontics, streamlines surgical work. Micro-instruments are placed in a sterile container or tray to avoid damage. During sterilisation or transit, the tips of the instruments must not come into contact with each other. Needle holder, they come in a variety of sizes and are designed to grab very thin needles. Their jaws are smooth, resulting in a straightforward and controlled knot. The most popular needle holders are 14 cm and 18 cm.[11] The needle holder tip should be 1mm for suturing 5-0 and 6-0 sutures, and 0.3 mm for suturing 8-0 and 10-0 sutures. Sutures and microsurgical needles to prevent breaking, needles have high flexural and ductile strength. Curved needles fit better into small areas. In periodontal surgery, needles with a 3/8 or 12 curve circular and an arc length of 8-15 mm are preferable. Needles ranging from 6-0 to 9-0 are commonly used.[12]

Indications: Microsurgical Periodontal Surgery:[13,14.] Minor Surgical Procedure, Flap Surgery, Regenerative surgery, Muco-gingival / Perio-plastic surgery.

Passive wound closure represents one of the three fundamental principles in microsurgery. Achieving precise primary closure of the wound edges is crucial for obtaining the desired outcome. Ideally, incisions should be nearly imperceptible, and they should be closed using meticulously positioned, small sutures that minimize tissue trauma and bleeding. Advances in suture materials and techniques have led to the development of sutures tailored for specific procedures across various surgical specialties, with dental procedures benefiting from these innovations.

In microsurgery, fine-gauge needles, ranging from small to extremely small, are used. These needles are designed to provide optimal stability when held by a needle holder, a critical factor influencing the entire suturing process. It's essential for the surgeon to have complete control over the procedure, particularly when passing the needle through the tissue. Therefore, the needle holder must be appropriately sized to match both the needle and the selected suture material. This ensures that the surgeon maintains the highest level of control and precision throughout the suturing process.

To facilitate passive wound closure, microsurgery relies on meticulous, minimal invasive entry incision design and dissection. The site is then closed utilising the proper fundamental techniques, with the aim of achieving both primary and passive wound site closure. (Price PB, 1948).[15]

In Mucogingival Surgery:

All these techniques yield varying degrees of therapeutic benefits due to their sensitivity to the operator's skill and the specific technique employed. Microsurgical

approaches, which require an extended period of learning and practice to achieve desired treatment outcomes, offer a more compatible method for complete successful muco-gingival surgical treatment results.

In the field of periodontics, microsurgery has proven to be a valuable approach for improving the predictive results of gingival transplantation techniques used in root coverage treatment. It also helps in reducing surgical damage and postoperative discomfort. When combined with accurate diagnosis, microsurgical techniques significantly enhance the predictability of achieving complete root coverage in various cases of mild to moderate marginal tissue recession abnormalities. Moreover, even in cases of class III and class IV marginal recession, where conventional surgery often yields partial root coverage results, microsurgery can lead to substantial improvements in outcomes.

Papillary Reconstruction Procedure:
The restoration of missing interdental papillae remains difficult. Microsurgical treatment is an atraumatic approach for positioning donor tissue under a deficient interdental papilla. Surgical magnification and microsurgical devices are important because to the small size of the interdental papilla and the limited access.[16]

Root Coverage Procedures:
The success of the root covering operation is dependent on the surgeon's dexterity, excellent visualisation of the working region, and, of course, an atraumatic surgical technique. A surgical microscope can meet all these requirements. To maximise treatment outcomes, it is necessary to regulate aspects impacting the degree of coverage, such as root preparation, sensitive tissue handling, tissue biotypes, and thorough plaque control.[17]

Minimal Invasive Surgery in Implant Therapy:

Techniques that give function, aesthetics, and comfort using a minimally invasive surgical approach are widely recognised among clinicians and patients in the modern era. Many clinicians suggest trans-gingival (flapless) implant surgery to meet this need. This method can be utilised to ease the implant placing procedure.[18]

The one-piece implant technique promotes improved tissue recovery by improving gingival mucosal adhesion to build a collar that is adequate for healing and adapting to the surface of implant, so eliminating a second surgical treatment (Prithviraj DR, et al 2013).[19] Single unit implant prosthetic approach allows the normal structure of the Peripheral tooth tissues to be preserved by allowing a endline preparation that follows the contour of the gingival margin, resulting in a better keeping of the mucosal seal (Barrachina-D'ez JM et al in 2013).[20] The success rate of single unit immediate loading implants is comparable to that of delayed loading implants (Shigehara S, et al in 2014).[21]

Sinus Floor elevation:
Numerous authors have proposed modifications to conventional techniques, leading to the rise in popularity of "Minimally Invasive Techniques". One notable advancement in the realm of sinus augmentation is the "Sinus Lift System" an example of minimal invasive indirect sinus lift tools. When combined with Platelet-Rich Plasma (PRP) and Tricalcium Phosphate (TCP), this procedure becomes even more reliable, potentially accelerating bone production and sinus elevation.

It is reasonable to assert that elevation of sinus floor using the "sinus-lift system" is a dependable method for getting significant sinus lift during augmentation procedures. This approach, involving sinus lift prior to implant placement, is poised to play a more prominent role in the future due to its evident advantages. Minimal invasive technique provides successful implant

procedure and maximize the augmentation. This proposed technique is minimally invasive, reduces procedural time, enhances the precision of implant dentistry with predictable outcomes, and enhances the comfort of implant patients.[22]

Wound Healing in MIPS

Microsurgery promotes a healing process. Reduces the formation of granulation or scar tissue. Research suggests that wounds treated with microsurgery typically heal within 2 days. In contrast secondary wound healing takes longer as new tissue needs to be generated to fill the gaps at the wound's edges. The reduced surgical trauma, during microsurgery leads to cell damage, necrosis, inflammation and pain.

Microsurgery promotes healing with granulation or scar tissue formation. Studies indicate that wounds treated with microsurgery typically heal within 48 hours. In contrast secondary wound healing takes longer as new tissue needs to be generated to cover the gaps at the wounds edge. The advantage of microsurgery is that it causes cell damage due, to reduced trauma.

The Transition Sequence:

Periodontists are now able to receive training in periodontal microsurgery. However, microsurgery training differs from other types of continuing education courses. First and foremost, the courses are practical rather than academic. Their primary educational emphasis is on the clinical skills required for excellent microsurgical technique. To guide students' skills from beginner to advanced levels, a programme requires at least two days of rigorous training with direct one-on-one instruction. Movement education focusses the mind and enhances the neurobiology of learning to new heights of performance and achievement. As the twenty-first century progresses, such learning approaches will play an increasingly essential role in teaching periodontists for microsurgery as it enters the mainstream of periodontal therapy.[23]

A practitioner who aspires to learn microsurgery must become visually acclimated to the microscope. Visual movement of the instruments without reference to surrounding cues (known as kinaesthetic movement) necessitates a slower, more nuanced movement. New microsurgical skills, such as tool grip and posture, must be learned by the practitioner. Structured training creates an optimal setting for developing these abilities. After training, the practitioner might gradually integrate microsurgery into his or her office practise.

Common errors in the use of surgical microscope are using magnification that is too high, inadequate task sharing between surgeon and assistant, Lack of practice. The technology currently considered cutting-edge for both non-surgical and surgical minimally invasive periodontal therapy is likely to be seen as primitive or outdated in the next 30 years. The potential for advancements in periodontal therapy seems boundless, with a strong likelihood that treatment procedures will become progressively more effective and less invasive.[24]

Conclusion

Minimally invasive periodontal surgery (MIPS) is becoming increasingly important as medicine and dentistry pursue less invasive treatment options. The use of microscopes allows for precise and detailed information for diagnosis and treatment. MIPS has many benefits, such as improved aesthetics, faster healing, and less patient discomfort. Utilizing endoscope-assisted root planning and regenerative surgery is proving to deliver superior results with reduced patient morbidity when compared to conventional techniques. The goal of any treatment is the regeneration of lost tissue with minimal post-operative issues, which

MIPS is proving effective in achieving. Specific training, instruments, and materials are required for a successful minimally invasive approach. Further studies are necessary to determine if MIPS can substitute conventional methods while accomplish similar or better results.

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Comparison of Layers of Twak and Layers of Skin

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Abstract
'Twak' as per Ayurvedic science means which encloses the whole body. Joseph Listre said, 'Skin is best dressing'. Twak is updhatu of Mamsa which forms the outer covering of the body and protects the body from external factors such as heat & cold. It is an important organ of integumentary system which envelops underlying tissues & organs. Ayurveda mentions twak as sparshanaindriya and different layers of twak are mentioned by Acharyas. Understanding each layer is still unclear with reference to layers of skin mentioned by contemporary science. There is a need to understand the different layers of twak & skin, their structural, functional and developmental interpretation and to correlate between them.
Keywords: Twak, Sparshanaindriya, Updhatu

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Introduction

In Ayurveda the word Twak is used for Skin. Twak is called because it covers the body. Acharya Sushruta described the process of formation of Twak in developing foetus. After fusion of Shukra and Artava, twak develops just as layer of Santanika (Scum) appears in the boiling milk which gradually increases in thickness, in similar manner the seven layers of skin are formed over surface of foetus of body.[1] During the formation of Garbha, differentiation of the layers of the skin takes place and is produced by all the three doshas, particularly by the Pitta dosha. Charaka described twak as the Matruja Bhava (maternal factor) which is one of the six bhava essential in the development of foetus. Whereas Vagbhatta opinei Twak derived from Rakta by action of rakta dhatwagni, it gets dried up to form the skin, like the deposition of cream on the surface of boiling milk. Acharya Charaka mentioned six layers of twak. Only first two layers are named such as Udakadhara and Asrugdhara.[2]

Acharya Sushruta has described seven layers of Twak. He mentioned the thickness of each layer along with the conditions affecting those layers.[3] Acharya Vagbhata has mentioned seven layers of twak similar to Sushruta. He has not given any description regarding it, commentator Arunadatta and Hemadri have named them as per Sushruta.[4]
test arteriovenous fistula puncture pain level among patients undergoing heamodialysis with their selected demographic variables.

Sharangadhara has mentioned seven layers of twak along with diseases affecting them.

The first six layers are same as that of Sushruta, but a seventh layer is named as Sthula which is site of Vidradhi.[5] There is different opinion regarding the number of layers of twak. The layers of twak explained by different Acharyas have been tabulated (Table 1).

Table 1: Layer of Twak as per different Acharyas

Layers	Charaka[6]	Sushruta[7]	Vagbhata[8]	Arunadatta[8]	Sharangadhara[9]	Bhavaprakasha[10]
Prathama	Udhakadhara	Avabhasini	1st	Bhasini	Avabhasini	Avabhasini
Dwitiya	Asrugdhara	Lohita	2nd	Lohita	Lohita	Lohita
Tritiya	Sidhma, Kilasasambhava adhistana	Shwetha	3rd	Shwetha	Shwetha	Shwetha
Chaturtha	Alaji, Vidradhisambhav aadhistana	Tamra	4th	Tamra	Tamra	Tamra
Panchami	Dadru, Kushtasambhava adhistana	Vedini	5th	Vedini	Vedini	Vedini
Shashthi	If this layer is injuired, leads to Andhatwa and Tama pravesha	Rohini	6th	Rohini	Rohini	Rohini
Sapthami		Mamsadhara	7th	Mamsadhara	Sthula	Sthula

Sharangadhara has mentioned seven layers of twak along with diseases affecting them. The first six layers are same as that of Sushruta, but a seventh layer is named as Sthula which is site of Vidradhi.[5] There is different opinion regarding the number of layers of twak. The layers of twak explained by different Acharyas have been tabulated (Table 1).

The skin is the largest organ of the body with a total area of 20 sq feet and weighs 4.5 – 5 kg and about 7 % of total body wt. Skin is known as 'The First line of Defence' as it protects us from microbes and other invading elements. It is part of integumentary system that contributes to homeostasis by protecting the body and helping to regulate body temperature. It allows us to sense pleasurable, painful and other stimuli in the external environment. Skin and its components are entirely derived from ectoderm & mesoderm. Skin is composed of three layers outer Epidermis, Dermis & Hypodermis.[6,7] (Table 2)

Discussion

Acharya Sushruta, Vagbhata, Bhavprakasha & Sharangadhara had mentioned seven layers of twak. While Acharya Charaka, Bhela & Astanga Sangraha mentioned six layers of twak. There is difference in opinion regarding layers of twak due to prospective vision of surgeon & physician.

Table 2: Layers of Skin and thickness

Layer of Skin	Sub-layers	Thickness
Epidermis	Stratum corneum	10-30mm
Thin skin –4 layers, 0.1mm	Stratum lucidum	100 mm
Thick skin – 5 layers 1-2mm	Stratum granulosum	100mm
	Stratum spinosum & S. basale	100mm
Dermis	Papillary layer	100 mm
	Reticular layer	

Prathama Avabhasini

Acharya Sushruta called outermost layer of Twak as Avabhasini with thickness 18/20th of vreehi and is seat of diseases like Sidhma & Padmakantaka. Dalhana mentioned first layer is responsible for exhibition of Gaura, Shyamadhi Varna & fives types of Prabha (glory) & Chaya (shades) of body with help

of Bhrajaka Pitta. Acharya Charaka & Vrddha Vagbhatta named outer layer as Udakadhara. As the name suggest it holds Udakadhatu. Indu depicts that this layer carries Udakadhatu & prevents outflow & maintain ardratabhava i.e moisture content of twak on its surface. Vagbhatta stated that 1st layer as Bhasini which is similar feature as explained by Astanga Sangraha & Charaka. As the layers superficial to Malpighi are opaque, exhibition of complexion is done by Stratum corneum, hence Avabhasini may be correlated with Stratum corneum. The corneal layer is made up of scale like flattened epithelium which consist of keratin filaments this make it highly resistant to permeation by water. So as the result it prevents the water loss from body and due to this reason Acharya Charaka called it Udakadhara.

Dwitiya Lohita

Sushruta named second layer of twak as Lohita having thickness 16/20th of Vreehi, and is adhistana of Tilakalaka, Nyaccha & Vyanga. Charaka & Vriddha Vagbhatta called the second layer as Asrugdhara. Indu explains this layer as Rudhantva Asram i.e it holds the blood and prevents outflow of Raktadhatu from the body. Hemadiri describes this layer as Lohini. Stratum lucidum layer consists of homogenous distributed cell layers with indistinct cell boundary which give it clear/lucid appearance. The change in amount of Hb%, bilirubin is reflected through this layer as the pallor or icteric look of skin. So Acharya has opinion as Lohita and / or Asrgdhara for this layer.

Tritiya Shweta

Sushruta called third layer as Shweta, it is having thickness of 12/20th of Vreehi and is adhisthana for Charmadala, Ajagalika and Mashaka. Charaka & Vrdhha Vagbhata mentioned third layer is seat of Sidhma & Kilasa. Astanga Hrudaya describes the third layer as site of Sidhma & Shwitra. Underneath the Stratum lucidum is Stratum granulosum, it is made up of 2-5 layers of flattened cells containing the granules in their cytoplasm. The kerato-hyaline granules are numerous in this layer which binds the keratin filaments in thick layer.

Chaturthi Tamra

Sushruta mentions the fourth layer of twak as Tamra. It lies beneath the Shweta and has thickness 8/20th of Vreehi. It is the seat of Kusta and Kilasa. Charaka mentioned the fourth layer as Dadrukushta adhistana. Astanga Sangraha & Hrudaya stated the fourth layer as adhistana of Sarvakushta. Sarangadhara and Bhavaprakasha stated Tamra as site for Kilasakushta. The chaturthi layer we can take both Stratum spinosum and Stratum basale because below the Shweta (S. granulosum) is Stratum spinosum. Melanin pigment released by melanocytes which lies in Stratum basale & scattered in Stratum spinosum which determines the complexion of an individual. So, Acharya opines 5th layer as Tamra with Stratum spinosum & Stratum basale.

Panchami Vedini

Sushruta mentions fifth layer as Vedini. As the name suggests, it is concerned with perception of touch, pain, heat and cold. It is about 5/20th of Vreehi in thickness. It is adhistana for Kusta & Visarpa. Charaka & Vagbhata describes the 5th layer as adhistana for Alaji & Vidradhi. Hemadiri stated this layer as Twagvedini as well as Rogakarini. Sharangadhara & Bhavaprakasha describe these layers as site for Sarvakushta & Visarpa. This layer is responsible for perception exterior-ceptive information, since it is incorporated with many receptors such as Meissner's corpuscles, Pacinian corpuscle, Ruffinis corpuscles, free nerve ending etc. Kushta and Visarpa affecting this layer also produce in organization of papillary layer of dermis. So, the Acharya opines this layer as Vedini which corresponds to papillary layer of dermis.

Shasthi Rohini: Sushruta states the 6th layer of Twak as Rohini which is equal to 1 Vreehi in thickness. It is adhistana for Granthi, Apachi, Galaganda, Arbuda & Shleepada. Charaka mentioned this layer as Arumshiadhistana. Chakrapani described that sudden injuiry to this layer leads to Tamayathi andhaevaie feeling of darkness in front of eye due to sudden loss of consciousness. AcharyaVagbhata stated 6th layer as Pranadhara. Indu stated that any injuiry to this layer leads to life threatening condition Tama Praveshaie feeling of blindness for short period, it is prime location of Arumshiie small boils, blackish red in appearance commonly found in small joints and very difficult to treat. Rohini name suggest, that is responsible for wound healing process i.e Vrana Ropana Karma, this layer plays major role in formation of granulation tissue, fibrous tissue during the wound healing. Due to this Acharya opines this layer as Rohini corresponds to Reticular layer of dermis in contemporary science.

Sapatami Mamsadhara

Acharya Sushruta mentions 7th layer as Mamsadhara. It is thickest layer measuring about 2 Vreehi. It is adhistana for Bhagandhara, Vidradhi, Arsas. Sarangadhara & Bhavaprakasha describes the 7th layer as Sthula, having thickness of two vreehi, it is site of Vidradhi. Adhamalla mentioned Sthula, it is site for Vidradhi, Bhagandhara and Arshas. Mamsadhara Twak explained by Sushruta can be correlated with hypodermis as it comprises of blood vessels, lymphatics and adipose tissue. It is the superficial fascia which envelopes the underlying muscle and does the dharana of the muscle, so called Mamsadhara.

Formation of Twak:

Twak is the Upadhatu of Mamsa.[12] Sushruta described that after fertilsiation of Sukra & Shonita. Twak develops just as Santanika which forms in layer wise and gradually increase in thickness, in the similar way seven layers of the Twak are formed and deposited rapidly in the same manner as the layers of Scum are formed and accumulates on the surface of the boiling milk.[13] Vagbhata opinion that the twak is formed from the Rakta. After the Paaka of Rakta by its Dhatwagni, it gets dried up to form the skin, like deposition of scum on the surface of boiling milk.

Out of two layers of skin, the epidermis is a superficial epithelial tissue derived from surface ectoderm & dermis is a deeper layer composed of dense irregularly arranged connective tissue derived from mesenchyme. Skin structures vary from one part of the body to another. The embryonic skin at 4-5 weeks consists of a single layer of surface ectoderm overlying the mesoderm. During the first & second trimesters of pregnancy there is an increment in epidermal thickness. The cells of surface ectoderm proliferate and form a layer of squamous epithelium, the periderm and basal layer. The cells of the eperiderm continually undergo keratinization and desquamation and are replaced by cells arising from the basal layer. Replacement of peridermal cells continues till the 21st week, thereafter, the periderm disappears and the Stratum corneum forms. Proliferation of cells in the Stratum germinative also forms epidermal ridges, which extend into the developing dermis. The transformation of the surface ectoderm into a multi-layered epidermis result in the formation of different layers of epidermis. Skin is classified as thick or thin based on the thickness of the epidermis.[15] (Table 3)

Melanoblasts are derived from neural crest & migrate in Stratum basale; Lanerhans cells are derived from the bone marrow and migrate into the epidermis. Merkel cells are of uncertain origin and is associated with free nerve endings.[16]

The dermis mostly develops from mesenchyme which arises from the somatopleuric layer of lateral mesoderm

plate; however, some of it is derived from the dermatomes of the somites. By the 11th week, the mesenchymal cells produce collagenous and elastic fibres. As the epidermal ridges form, the dermis projects into epidermis, forming dermal ridges that interdigitate with the epidermal ridges. Sensory nerve ending, tactile receptors and vascular element develops in the ridges.[17]

Table 3: Layers of Skin as per Ayurveda and possible modern correlation

Layers	Twak layer	Subdivision of layer of Skin	Skin layer
Prathama	Avabhasini	Stratum corneum	Epidermis
Dwitiya	Lohita	Stratum lucidum	
Tritiya	Shweta	Stratum granulosum	
Chaturthi	Tamra	Malpighian layer	
Panchami	Vedini	Papillary layer	Dermis
Shasthi	Rohini	Reticular layer	
Saptami	Mamsadhara	Subcutaneous tissue and Muscular layer	Hypo-dermis

The layer of skin derived gradually in layer wise during intrauterine life of foetus. These develop two types of skins in foetus body, thick skin covers the palms & soles; it consists of 5 layers in epidermis, it lacks hair follicle, arrector muscles of hairs and sebaceous glands, but it has sweat glands. & thin skin covers most of the rest of the body; it lacks the Stratum lucidum layer in epidermis; it contains hair follicles, arrector muscles of hair, sebaceous glands & sweat glands.

Measurement of layer of Twak:

Dalhana describes the total thickness of Twak as Angustha Udara Pramana which is equal to Shad YavaPramanaie thickness of six barley grains together. The parameter for thickness is applicable for fleshy area not for bony are like Sukshma Anguli and Lalaata (forehead). The motive behind describing thickness of each layer of twak is for performing various surgical interventions such as abdominal tapping should be done in Angusta Udara Pramana by Vrihimukha Yantra in Jaludhara.

The classical description regarding the pramana of each layer of Twak, on adding the pramana of each layer we get 6 yava. But to match with contemporary science is difficult. Also, diseases which has its seat in different layer is difficult to correlate with contemporary science. So, it can be a subject further study.[18]

Conclusion

Based on comparative study, the seven layer of Twak namely, Avabhasini, Lohita, Sweta, Tamra, Vedini, Rohini & Mamsadhara respectively can be correlated with Stratum corneum, Stratum lucidum, Stratum granulosum, Stratum malpighan, Papillary layer of Dermis, Reticular layer of dermis & Hypodermis based on simile of their structure functional and applied aspect. Regarding the formation of the Twak all layers of Twak does not appear at once rather they appear layer by layer during intrauterine life of the foetus which is similar to appearance of cream in the boiling milk as mentioned by the Acharyas.

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Revolutionizing Drug Discovery: The Role of Artificial Intelligence in Modern Drug Design

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Abstract:

The traditional drug discovery process is slow, expensive, and prone to high failure rates, with timelines of 10–15 years and costs reaching $1–2 billion. Recent advancements in artificial intelligence (AI) have revolutionized drug design by enabling the analysis of vast biomedical datasets, identifying patterns, and making predictions that streamline and optimize the drug discovery pipeline. This article explores the transformative role of AI methodologies, including Machine Learning (ML), Deep Learning (DL), Natural Language Processing (NLP), and generative models, in accelerating target identification, lead compound optimization, and predicting drug toxicity or efficacy. AI applications in drug repurposing, de novo drug design, and the prediction of drug-target interactions are discussed, showcasing significant reductions in time and resource requirements. The article also highlights critical challenges, such as data quality, model interpretability, and regulatory concerns, which must be addressed to fully realize the potential of AI in drug discovery. With continued advancements and collaboration between computational and pharmaceutical sciences, AI promises to revolutionize drug development, paving the way for personalized and precision medicine.

Keywords: Artificial Intelligence (AI), Deep Learning (DL), Natural Language Processing (NLP), Drug Repurposing, Lead Compound Optimization, Drug-Target Interactions, De Novo Drug Design.

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1. Introduction

The traditional drug discovery process is notoriously slow, expensive, and has a high failure rate. On average, bringing a drug from the initial discovery phase to market approval takes around 10-15 years and costs between $1-2 billion.[1] The complexity arises from several factors, such as identifying suitable drug targets, designing compounds with desired therapeutic effects, and conducting multiple phases of clinical trials to ensure safety and efficacy.

AI has emerged as a revolutionary tool in drug design, offering the ability to analyze vast amounts of biomedical data, recognize patterns, and make predictions that were previously unattainable.[2] By leveraging computational power, AI can expedite target identification, optimize lead compounds, and even predict drug toxicity or efficacy, all while cutting down the time and resources required.[3] This section introduces the growing role of AI in transforming how new drugs are designed and the promise it holds for the pharmaceutical industry.

2. Methodologies in Drug Design

2.1 Machine Learning (ML)

Machine Learning (ML) involves using algorithms that allow computers to learn from historical data and make predictions or decisions without being explicitly programmed. In drug design, ML algorithms are particularly effective for analyzing large datasets from biochemical assays, clinical trials, or genomic studies to predict drug-target interactions, identify off-target effects, or optimize compounds for improved potency and reduced side effects.[3]

For example, supervised learning algorithms can be trained on datasets of known drug molecules and their biological activities to predict whether a new compound will likely bind to a particular target. Similarly, unsupervised learning can cluster chemical compounds based on their properties, aiding in drug classification and repurposing.

2.2 Deep Learning (DL)

Deep learning (DL), a subset of ML, is ideal for processing more complex data, such as 3D molecular structures and protein-ligand interactions. DL models, like convolutional neural networks (CNNs) or recurrent neural networks (RNNs), learn multiple layers of representation from raw data, allowing them to model more intricate biological systems.[4]

DL models have revolutionized tasks like structure-based drug design,[5] where 3D models of molecular interactions are used to predict how well a drug molecule will bind to its target protein.[6] These models can also screen vast chemical libraries, analyzing millions of potential drug candidates much faster than traditional methods.[6]

2.3 Natural Language Processing (NLP)

Natural Language Processing (NLP) enables AI to process and analyze vast amounts of unstructured data, such as scientific papers, patents, or clinical trial records. NLP algorithms extract key information from texts, such as new drug targets, mechanisms of action, or side effects, providing insights that can guide the drug discovery process.[7]

NLP is particularly useful for drug repurposing, where AI systems scan existing literature and clinical data to identify new uses for approved drugs, shortening development timelines by bypassing early-phase testing.[8]

2.4 Generative Models

Generative models, such as Generative Adversarial Networks (GANs) or Variational Autoencoders (VAEs), are used to create novel drug molecules. These models can explore vast chemical spaces to suggest entirely new compounds that meet predefined criteria, such as binding affinity, solubility, or toxicity profiles.[9]

For instance, VAEs can learn the underlying distribution of drug-like molecules and generate new, chemically valid compounds, while GANs can create novel molecular structures by pitting two

neural networks against each other to refine output quality.[10]

3. Applications of AI in Drug Design

3.1 Lead Compound Identification

Identifying lead compounds is one of the most critical steps in drug design, where AI significantly accelerates the process. AI-based algorithms use data from high-throughput screening (HTS) experiments to identify molecules that can potentially interact with a biological target. Virtual screening powered by AI models allows the evaluation of large chemical libraries, reducing the need for extensive laboratory-based testing.

For example, AI models can predict the binding affinity of drug candidates to target proteins, significantly reducing the number of compounds that need to be synthesized and tested in the lab.[11]

3.2 Drug Repurposing

AI excels in drug repurposing by analyzing existing drugs and their interactions with various targets, predicting new therapeutic applications. Repurposing approved drugs for different diseases saves time and resources since much of the safety testing has already been completed.[11]

Using AI tools like deep learning models and NLP, researchers have repurposed existing drugs for conditions ranging from rare diseases to cancer, significantly reducing the overall time to market.[12]

3.3 Prediction of Drug-Target Interactions

Predicting drug-target interactions is a fundamental aspect of drug design. AI-driven models, such as structure-based or ligand-based approaches, predict how small molecules (drugs) will interact with biological macromolecules (proteins or DNA). AI can model these interactions based on known structures of the drug and target, helping researchers to identify the best candidates for further development.[13] For example, structure-based models predict the interaction by docking simulations, where the AI algorithm fits a drug molecule into the binding site of a target protein and calculates the interaction strength.[14]

3.4 Optimization of Drug Properties

AI is used to optimize pharmacokinetic (PK) and pharmacodynamic (PD) properties of drug candidates. These properties include how a drug is absorbed, distributed, metabolized, and excreted (ADME), as well as its toxicity.[15] AI models can predict these parameters early in the drug development process, ensuring that only the most promising compounds move forward. For example, AI tools are used to predict a compound's solubility, permeability, and potential for toxicity, all of which are critical for successful drug candidates.

3.5 De Novo Drug Design

AI models, particularly generative algorithms, are now capable of performing de novo drug design, where they generate entirely new molecular structures from scratch. The algorithms explore vast chemical spaces and propose new molecules that have specific therapeutic properties. For example, AI-generated molecules for cancer treatments can be designed with predefined properties such as high affinity for a particular target and minimal toxicity.[16]

4. Challenges in AI-Driven Drug Design

4.1 Data Quality and Availability

AI systems are only as good as the data they are trained on. In drug design, high-quality, diverse, and comprehensive datasets are critical for building accurate AI models.

However, access to such datasets can be limited due to privacy concerns, proprietary restrictions, or inconsistencies in data collection methodologies. Additionally, biases in data can lead to poor model generalization, reducing the accuracy of predictions.[17]

4.2 Interpretability of AI Models

One major challenge with AI, especially deep learning models, is their "black box" nature. These models are often difficult to interpret, meaning that researchers may not fully understand how or why a particular prediction is made. To gain wider acceptance, AI models need to offer greater transparency, so that their predictions can be trusted and validated by experts in the field.[18]

4.3 Regulatory and Ethical Concerns

As AI becomes more integrated into drug design, regulatory agencies like the FDA will need to establish frameworks for evaluating AI-generated results. Ethical concerns, such as the ownership of AI-designed molecules and the responsibility for AI-driven decisions, must also be addressed.[19]

4.4 Integration with Experimental Validation

While AI models can make accurate predictions, these predictions must be validated in the lab through biochemical assays, animal models, and eventually clinical trials. The integration of AI predictions with experimental validation is critical to ensure the safety and efficacy of AI-designed drugs.[20]

5. Discussion

The integration of artificial intelligence (AI) in drug discovery marks a paradigm shift in the pharmaceutical industry. Traditional drug design is fraught with challenges, including extensive timelines, exorbitant costs, and high attrition rates. AI technologies, by contrast, offer solutions that enhance efficiency, reduce costs, and improve success rates across various stages of drug development.

5.1Key Contributions of AI

AI's ability to analyze complex datasets, uncover hidden patterns, and make accurate predictions has revolutionized target identification, lead compound optimization, and drug property prediction. Machine Learning (ML) and Deep Learning (DL) have been particularly impactful in predicting drug-target interactions and optimizing molecular structures. Similarly, Natural Language Processing (NLP) and generative models have streamlined processes like literature analysis and de novo drug design, respectively.For instance, DL's capacity to interpret 3D molecular structures and simulate protein-ligand interactions has significantly enhanced structure-based drug design. Generative models, such as GANs and VAEs, have expanded the scope of chemical space exploration, enabling the generation of novel compounds with desired therapeutic properties. Furthermore, AI-driven virtual screening reduces the need for extensive experimental assays by prioritizing promising candidates early in the pipeline.

5.2 Applications and Benefits

AI-driven tools have successfully expedited drug repurposing, identifying new therapeutic applications for existing drugs and bypassing early-stage safety testing. In predictive toxicology and pharmacokinetics/pharmacodynamics (PK / PD), AI has proven invaluable for anticipating adverse effects and optimizing drug profiles, ensuring only viable candidates progress to clinical trials. These advancements not only accelerate drug

development but also enhance the precision of therapies, particularly in the context of personalized medicine.

5.3 Challenges and Limitations

Despite its transformative potential, several challenges limit the widespread adoption of AI in drug design. Data quality and availability remain significant obstacles, as AI models require large, diverse, and unbiased datasets for training. Additionally, the interpretability of AI predictions, especially in deep learning models, remains a hurdle, as their "black-box" nature raises concerns about the reliability and transparency of results.

Regulatory and ethical concerns also need attention. Clear frameworks for evaluating AI-generated outputs, data privacy considerations, and questions of intellectual property ownership for AI-designed molecules must be addressed. The integration of AI predictions with experimental validation is another critical aspect to ensure the robustness of outcomes.

5.4 Future Directions

The future of AI in drug discovery is promising, with opportunities for real-time drug optimization, improved automation in laboratories, and the development of precision therapies for rare and complex diseases. Continued advancements in algorithms, coupled with interdisciplinary collaboration and robust regulatory frameworks, are essential to unlocking the full potential of AI.

6. Conclusion

AI has emerged as a powerful tool, addressing many limitations of traditional drug discovery processes. While challenges persist, the ongoing evolution of AI technologies, supported by collaborative efforts, can transform the landscape of drug development, ultimately benefiting both pharmaceutical research and global healthcare.

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A Rare Case Report of Congenital Adrenal Hyperplasia: 46XX at Tertiary Care Centre, Visnagar, North Gujarat.

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Abstract

This report presents a rare case of pure classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency in a 22-year-old woman with a 46 XX genotype. The patient exhibited virilism, excessive hair growth, and primary amenorrhea with absent secondary sexual characteristics. The diagnosis was confirmed by 17-hydroxyprogesterone testing and the Synacthen test. Treatment with hydrocortisone and spironolactone was followed by feminization surgery, leading to the development of secondary sexual characteristics, including breast development, a reduction in hirsutism, and the onset of regular menstruation.

Keywords: Congenital adrenal hyperplasia; 21-hydroxylase deficiency; Virilism; Syacthen test; Feminizing surgery; Hydrocortisone; Spironolactone

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Introduction

The most prevalent type of congenital adrenal hyperplasia (CAH), which is a collection of autosomal recessive illnesses, is 21-hydroxylase deficiency, which is defined by enzyme abnormalities in the adrenal steroidogenesis pathway. The disorder is caused by mutations in the CYP21A2 gene that codes for an enzyme called 21-Hydroxylase[1] which results in a high level of adrenal androgens or inadequate synthesis of cortisol and aldosterone. Due to excessive testosterone exposure during pregnancy, females with the severe type of classic 21-hydroxylase deficiency have virilized external genitalia at birth. This illness can have serious long-term health effects and potentially fatal adrenal crises if left untreated.

The uncommon appearance of a 22-year-old woman with pure classical virilizing CAH is described in this case report, underscoring the difficulties in diagnosis, treatment, and clinical care. To guarantee transparency and completeness, the report is prepared in accordance with the CARE criteria.[2]

Case Presentation

In her adult life, a 22-year-old woman from a non- consanguineous marriage visited our outpatient department. Her preliminary consultation with our team was for atypical sexual development (excessive hair growth) amenorrhea and unclear genitalia which

dates back to the time her mother found a genital bud at birth. Upon reviewing her medical history, no evidence of maternal exposure to androgens during pregnancy or salt loss syndrome was discovered. She visited numerous gynecologists for her issue, but she never obtained a satisfactory response. She eventually came to us about her issue. The clinical examination revealed excessive amounts of body hair growth, no breast growth, and a male morphotype.

The genital examination demonstrated a pair of distinct orifices below the clitoris (Prader II), non-fused smooth pigmented and symmetrical genital folds, clitoromegaly with peniform aspect that measured broadly around 5.5 cm in length and 2 cm in width, and no evidence of gonad palpation at the inguinal and fold levels (Fig 1 and 2). Her subjective Ferriman and Galleway Score of 29 indicated significant hirsutism, which was linked to virilization symptoms.

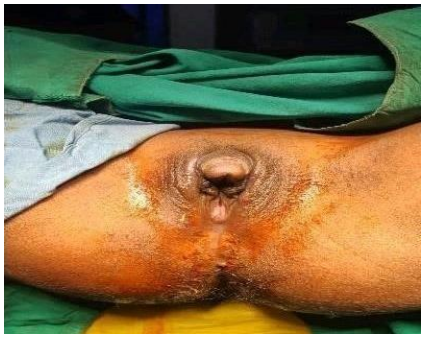

Fig 1 Pre-treatment photograph showing symmetrical, non-fused, pigmented vaginal folds, clitoromegaly with penniform appearance, and two distinct orifices beneath clitoris.

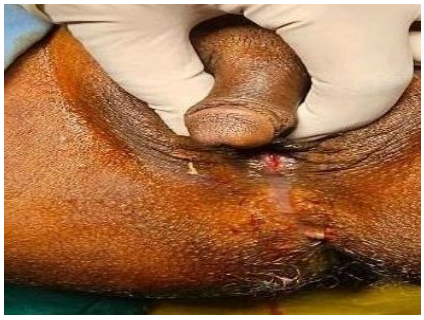

Fig 2: Pretreatment Photograph showing clitoromegaly and Pinniform appearance.

On 50 mitoses, the biological exploration using modal of karyotypes demonstrated a karyotype 46, XX, with testosterone levels of 367.55 ng/ml (CMIA), progesterone was 23.3ng/ml and estrogen (E2) was 3.3 pg/ml while DHEA 752.5 µg/dl (CMIA), and 17OH Progesterone subsequently synacthene stimulation T60 min: 354 ng/ml (VN< 10 ng/ml, radioimmunology), cortisol level was low, measuring 52 g/ml (CMIA). A hypoplastic uterus with uniform contours measuring 42 x 21 x 17 mm and macropolycystic ovaries measuring 23 mm on the left and 24 mm on the right were discovered by pelvic ultrasonography. An abdominal MRI scan revealed hypertrophy of the adrenal glands but no other abnormalities.

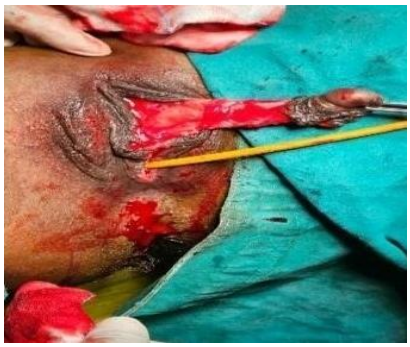

Fig 3: Illustrates the size of the clitoris, with a peniform aspect measuring 5 cm by 2 cm,

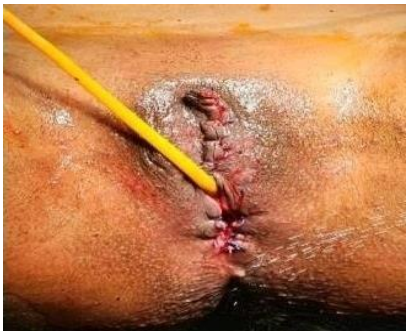

Fig 4: Clitoris appearance following clitoroplasty

Therapeutically, hydrocortisone replacement at a dosage of 10 mg at 8 am and 5 mg at 5 pm was to be administered in addition to dexamethasone at a dose of 0.5 mg/d at night. After three months she observed breast growth which was corresponding to stage S2 of Tanner, the

clinical examination revealed a minor decrease in hirsutism, a Ferriman and Gallaway score of 25 versus 29, and smaller in size clitoris measuring 5.5 cm against 5 cm. On a biological level, the 17 OHP went back to 168.6 ng/ml, and the testosteronemia dropped to 1.12 ng/ml from 3.69 ng/ml. At this point, the patient was admitted for vaginoplasty and clitoroplasty procedures. The surgery went smoothly and efficiently (Fig 3 and 4). Normal anatomical communication was established between the cervix and vagina. To avoid vaginal restenosis, she was encouraged for self-introduction of vaginal mold once a day.

Discussion

A collection of autosomal recessive illnesses known as congenital adrenal hyperplasia are brought on by total or partial abnormalities in one of the numerous steroidogenic enzymes that the adrenal glands use to synthesize cortisol from cholesterol. Steroid 21-hydroxylase, an enzyme encoded by the CYP21A2 gene, is deficient in over 95–99% of all CAH patients.[3] According to data from millions of babies screened globally, 1 in 10,000 to 1 in 20,000 live births had classic CAH.[4,5] With an estimated prevalence of one case per 200 people to one case per 1000 people, non-classic CAH is widespread throughout the world.[6]

The ambiguous genitalia associated with genetic females (46,XX) in neonates (Classical CAH) exemplify clitoromegaly and labioscrotal fusion. Signs and symptoms of dehydration, vomiting, weight loss, and shock (in extreme cases) are typical during a salt-wasting crisis. Early pubarche and advanced bone age are present in children, who have tall stature initial stages but subsequently short as a result of early epiphyseal closure. Adolescents and adults with non-classical CAH exhibit hyperandrogenism symptoms and indicators, including female infertility, hirsutism, acne, and irregular menstruation. Lack of 21-hydroxylase, a cytochrome P-450 enzyme necessary for the adrenal cortex's synthesis of cortisol and aldosterone, is caused by mutations in the CYP21A2 gene. This enzyme's deficit causes a domino effect. The overproduction of pituitary corticotropin, which results from low cortisol, causes the adrenal cortex to enlarge and increases the release of cortisol precursors, specifically 17OHP, and adrenal steroids, the primary one being D4-androstenedione. In the target cells, this androgen can subsequently undergo metabolism to produce testosterone and dihydrotestosterone.[7]

A complicated genomic structure is intimately linked to the genetic pathways causing 21-OH deficiency. Although there are more than 200 known CYP21A2 gene mutations, over 90% of HCS cases are caused by a small number of these changes, either by gene conversion or uneven recombination. CYP21A2 point mutations account for 70–75% of cases. Large deletions connected to an uneven recombination process or abnormal segregation during meiosis account for 20% of cases. De novo mutations are linked to 21-OH deficiency in 1%–2% of instances. Real-time quantitative PCR is used for molecular diagnosis, employing distinct primer pairs that are unique for the CYP21A2 gene and not the CYP21A1P pseudogene. Point mutations are then found by sequencing.[8]

Two phenotypes, simple virilizing (SV) and salt wasting (SW), are indicative of the classic form. The age of finding, sex, and type of HCS all affect the clinical presentation. Ambiguous external genitalia are present in all patients with classic 21-OHD.[9] Rarely, like with our patient, the diagnosis of the classic pure virilizing type is established late in childhood, adolescence, or adulthood. In most cases, the diagnosis is made at birth. Because hyperandrogenism disrupts the gonadotropic axis, it can lead to anovulation

or dysovulation, which can cause irregular menstruation, irregular cycles, or even infertility.[10] Any patient who presents with oligomenorrhea and/or hyperandrogenism should have the diagnosis brought up. With severe hirsutism, a male morphotype, primary amenorrhea, no breast development, and a peniform clitoris, the clinical picture in our patient was highly suggestive. The ovaries, fallopian tubes, and uterus all develop normally. In addition to confirming the existence of female genitalia, pelvic ultrasonography often reveals the emergence of micropolycystic ovaries as a result of hyperandrogenism. This should not be confused with micropolycystic ovary syndrome, which is an elimination diagnosis. In our instance, macropolycystic ovaries measuring 23 mm on the left and 24 mm on the right were discovered by pelvic ultrasonography beside this evaluation of bone age was done using a left- hand's X-ray.

Serum 17-hydroxyprogesterone, usually stimulated by synthetic ACTH, is still the gold standard for diagnosing CAH. Therefore, the diagnosis is confirmed by a baseline 17 OH progesterone value greater than 2 ng/ml or a concentration >10 ng/ml in the synacthen test.[4] When diagnosing the condition, CYP21A2 genotyping is seen to be a useful supplement to biochemical tests.[3] But in our case because of the patient's financial issues, the genetic investigation could not proceed.

Blocking hyperandrogenism and preventing or managing complications of classic form and its therapy are the two goals of managing it throughout adolescent and adulthood.[11] The most widely used glucocorticoid is hydrocortisone. Other glucocorticoids, including dexamethasone, prednisone, or prednisolone, have longer half-lives and offer a stable replacement action all day. Unfortunately, without a sufficient dosage of glucorticoids, it is difficult to achieve androgen secretion suppression, and as a result, there is a substantial risk of iatrogenic hypercortisolism. Regardless of the regimen, the choice between long-acting glucocorticoids, which have a higher risk of adverse effects, and physiological hydrocortisone, which is well tolerated but has limited control on androgen secretion, remains problematic. Plenadren, a novel slow-release glucocoticoides formulation, was just released, while Chronocort, another, is presently being researched. Although the medication has not yet received approval, this is another modified-release hydrocortisone formulation that is being developed. It is taken twice a day, at bedtime and at waking, and has been demonstrated to imitate normal circadian cortisol levels. In patients with congenital adrenal hyperplasia, a phase II trial showed greater suppression of morning 17-OH progesterone levels (and, consequently, nightly androgen output). Phase III trial results are still pending.[12] In our case, in addition to dexamethasone at a dose of 0.5 mg/d at night, hydrocortisone replacement was to be given at doses of 10 mg at 8 am and 5 mg at 5 pm.

The antiandrogenic effects of spironolactone, an aldosterone antagonist, are seen at doses between 100 and 200 mg/day. It works by blocking androgen receptors and inhibiting 5-α-reductase activity.[11] In our instance, we decided to use 100 mg of spironolactone each day for treatment. A reduction in hirsutism, a reduction in the size of the clitoris, and the onset of breast development were observed as improvements in the symptomatology following three months of carefully managed replacement therapy and anti-androgenic medication.

Apart from this for proper dehydration and electrolyte imbalance in an acute crisis (salt-wasting CAH), intravenous fluids should be administered. IV hydrocortisone should be used for stress dosage to replenish cortisol. Beside this for the management of mineralocorticoid deficit in acute crises,

sodium supplementation and fludrocortisone are recommended. Along with mineralocorticoids, glucocorticoids are used in chronic care to replenish cortisol and inhibit excessive androgen production (e.g., hydrocortisone in children, prednisone in adults). Bone age, blood pressure, and growth are periodically monitored. When it comes to surgical management, femaleizing genitoplasty—ideally done during infancy in females with ambiguous genitalia. Growth abnormalities, puberty progression, and metabolic consequences of steroid medication all necessitate for continual observation. For concerns related to gender identity and quality of life, psychosocial help is crucial.

Complications include - Growth abnormalities spurred by the overt or insufficient usage of glucocorticoids, stress or illness-induced adrenal crisis and psychological effects associated with ambiguous genitalia and fertility. Patients can live normal lives with early diagnosis and proper care. Because of early intervention, newborn screening programs have greatly improved outcomes.

Conclusion

We describe a 22-year-old female patient who sought our consultation due to a sexual development abnormality, primary amenorrhea, and ambiguous genitalia. The diagnosis of congenital adrenal hyperplasia in its classic pure virilizing form remains unchanged at this age, necessitating challenging and specialized medical attention. In order to permit proper growth, female puberty, and good fertility, it is crucial to make the diagnosis as soon as feasible.

Consent: The patient's parents gave their written informed consent for this case report and its associated photos to be published.

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Abbreviations:

CYP21-gene encoding 21-hydroxylase Cytochrome P-450 enzyme
CMIA-Chemiluminescent microparticle immunology
DHEA-dehydroepiandrosterone sulphate
17OPH-17 hydroxyprogesterone
ACTH - Adrenocorticotropic Hormone

How to cite the article:

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Manuscript Preparation and Submission Guidelines

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- Original Research Articles: Present new findings and contribute to the existing body of knowledge in integrative health.
- Systematic Reviews and Meta-Analyses: Summarize and synthesize existing research on a specific topic.
- Clinical Studies: Describe investigations that evaluate the effectiveness and safety of integrative health interventions.
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