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ASSESSMENT OF INTRAORAL CLINICAL SIGNS OF HYPERSENSITIVITY TO 4D NAM™ APPLIANCE IN CLEFT LIP AND PALATE INFANTS: A PROSPECTIVE STUDY

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ABSTRACT

Background: our-dimensional nasoalveolar molding (4D NAM) appliances fabricated using thermo-responsive TA-28 (Graphy Inc., Seoul, South Korea) resins enable continuous and controlled force delivery. However, concerns regarding intraoral hypersensitivity in infants remain inadequately explored.

Objective: To evaluate intraoral clinical signs of hypersensitivity associated with 4D NAM appliances in infants with cleft lip and palate.

Methods: A prospective observational study was conducted on 17 infants undergoing 4D NAM therapy. Appliances fabricated using Graphy TA28 were assessed for hypersensitivity using clinical indicators including blanching, erythema, edema, ulceration, and behavioural responses. Evaluations were performed at every 10-day intervals coinciding with sequential tray changes.

Results: No clinical signs of hypersensitivity, including blanching, erythema, edema, or ulceration, were observed at any evaluation point. However, persistent crying was not observed following insertion of subsequent appliances at 10-day intervals, indicating rapid adaptation to the therapy. Feeding tolerance remained satisfactory, shows positive suckling reflex during feeding and all infants accepted the appliances well without interruption of therapy or any adverse clinical events.

Conclusion: The 4D NAM appliances exhibited excellent intraoral biocompatibility, with no evidence of hypersensitivity reactions, supporting their safe clinical use in infants. Although mild transient behavioural discomfort was observed following initial appliance insertion, infants adapted rapidly, and subsequent appliances were well tolerated. These findings suggest that thermo-responsive shape-memory resin is a clinically safe and acceptable material for presurgical infant orthopaedics. As these observations are based on preliminary data, further investigations involving larger cohorts and extended follow-up periods are necessary to validate the long-term safety and clinical performance of this novel material.

KEYWORDS: 4D NAM, Cleft lip and palate, Hypersensitivity, Infant orthopeadics, Shape memory aligner, Soft tissue response.

INTRODUCTION

Cleft lip and palate (CLP) represent one of the most common congenital craniofacial anomalies, with significant functional, aesthetic, and psychosocial implications.[1] Early management of these patients requires a multidisciplinary approach, in which presurgical infant orthopeadics plays a crucial role in improving anatomical alignment prior to definitive surgical repair. Among these modalities, nasoalveolar molding (NAM) has gained widespread acceptance due to its ability to approximate alveolar segments, reduce cleft width, and enhance nasal symmetry, thereby facilitating improved surgical outcomes.[2]

Conventional NAM therapy relies on sequential manual adjustments of an acrylic molding plate combined with nasal stents to guide tissue remodelling. Although effective, this approach is technique-sensitive and dependent on frequent clinical visits. Furthermore, periodic activation may result in intermittent force application, which can contribute to localized mucosal irritation, pressure-induced ulceration, and variability in treatment response.[3,4] These limitations have prompted the exploration of alternative approaches that allow for more controlled and physiologic force delivery.

Recent advancements in digital orthodontics have introduced the concept of four-dimensional (4D) printing, wherein materials are designed to undergo controlled shape transformation over time in response to environmental

stimuli such as heat.[5] In the context of NAM therapy, for the first time ever the term '4D NAM' has introduced in this manuscript. 4D appliance was fabricated using thermo-responsive smart polymers such as Tera Harz TA28 offer the potential to deliver continuous, low-magnitude forces without the need for frequent manual adjustments. Tera Harz TA28, a shape-memory resin, has been specifically developed for orthodontic applications and demonstrates temperature-dependent activation at approximately intraoral conditions (37°C), enabling gradual and programmed force delivery.[6]

From a biological perspective, the response of oral mucosal tissues to mechanical stimuli is influenced by the magnitude, duration, and distribution of applied forces. Infants' oral mucosa is particularly delicate, with reduced keratinization and increased susceptibility to trauma compared to adult tissues.[7] Excessive or improperly distributed forces can lead to a spectrum of clinical manifestations ranging from transient blanching and erythema to ulceration and tissue breakdown. Therefore, evaluating tissue tolerance is essential when introducing new materials and technologies in infant populations.

Hypersensitivity reactions in the context of intraoral appliances are primarily assessed through indirect clinical indicators, as infants lack the ability to verbalize discomfort. Observable signs such as mucosal blanching, erythema, edema, and ulceration, along with behavioural responses including irritability, feeding difficulty, and excessive crying, serve as important diagnostic markers. Previous studies on conventional NAM therapy have reported varying degrees of soft tissue irritation, often attributed to localized pressure points or improper appliance adaptation.[8] However, the continuous and low-force characteristics of 4D appliances may theoretically reduce such adverse tissue responses.

In addition to mechanical considerations, material biocompatibility plays a critical role in determining intraoral tolerance. Materials must exhibit minimal cytotoxicity, low allergenic potential, and adequate surface smoothness to prevent plaque accumulation and mucosal irritation. Specifically, Tera Harz TA-28 has been shown to maintain patient safety and non-cytotoxicity when processed with standard 20-minute UV curing protocols for material thicknesses up to 6 mm.[9]

Another important consideration is the timing and method of clinical evaluation. Traditional NAM protocols involve frequent adjustments and monitoring[10]; however, 4D NAM therapy is designed around staged activation, often corresponding to periodic tray changes. Evaluating tissue response at standardized intervals—such as every 10 days during appliance replacement—provides a clinically relevant framework for assessing cumulative tissue effects and ensuring patient safety.

Despite the theoretical advantages of 4D NAM, there is a paucity of clinical studies investigating intraoral hypersensitivity and tissue response associated with these appliances. Most available literature focuses on the mechanical and technological aspects of 4D printing rather than its biological implications in infant patients. This gap in knowledge underscores the need for systematic clinical evaluation of soft tissue response to these novel appliances.

Therefore, the aim of the present study was to assess intraoral clinical signs of hypersensitivity associated with 4D NAM appliances fabricated using a thermo-responsive smart polymer in infants with cleft lip and palate. The study specifically evaluated mucosal changes and behavioural responses at regular 10-day intervals during sequential tray changes, providing insight into the safety and biocompatibility of this emerging technology.

MATERIALS AND METHODS

Study design

This prospective observational clinical study was conducted in the Department of Orthodontics and Dentofacial Orthopaedics in a dental college in Bhubaneswar. Written informed consent was obtained from the parents or legal guardians of all participating infants. The study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 17 infants diagnosed with unilateral or bilateral cleft lip and/or palate were included in the study. The Inclusion criteria were infants aged ≤3 months at initiation of therapy, non-syndromic cleft lip and/or palate, no prior presurgical orthopaedic intervention. Whereas syndromic clefts or associated craniofacial anomalies, infants with lack of parental compliance for follow-up visits were excluded from the study.

Maxillary 3D (three dimensional) scans were obtained using iTero lumina intraoral scanner (Align Technologies Inc., USA). This scanner having a scanner head width of 41.5 mm which offers its compact size to obtain maxillary scan in infants. The STL file then retrieved and opened in Direct Aligner Designer (DAD) software (Graphy Inc, Seoul, South Korea) for virtual planning of NAM appliance.

The appliances were fabricated using a thermo-responsive shape-memory resin (Graphy TA28) in a 3D printer (Uniz NBEE Dental 3D). This material exhibits temperature-dependent activation at approximately intraoral temperature (~37°C), enabling gradual and programmed force delivery. Post-processing procedures, including cleaning, curing, finishing, and polishing, were performed according to manufacturer recommendations to ensure smooth and atraumatic intraoral surfaces.

The initial appliance was inserted after verifying proper fit, retention, and extension. (Figure 1) Caregivers were instructed regarding appliance hygiene, insertion and removal, and feeding practices. They were advised to make the child wear the appliance continuously, except during cleaning.

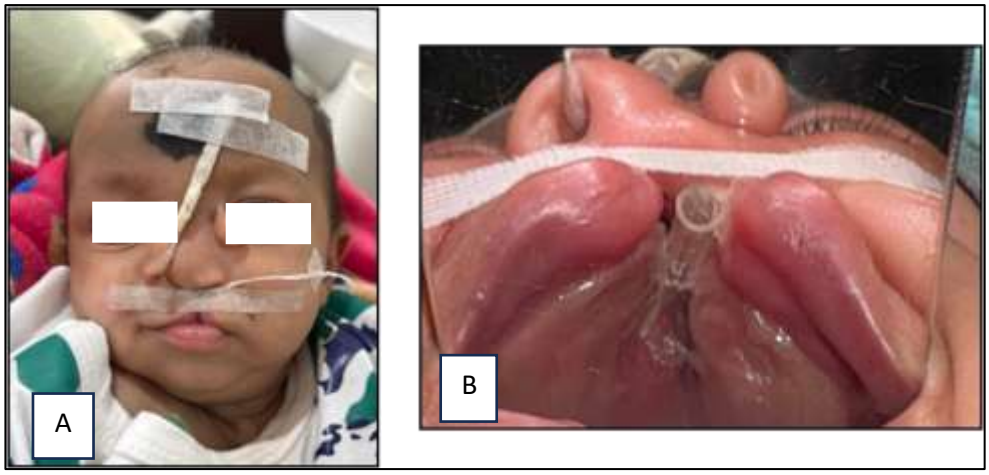

Figure 1: 4D NAM appliance. A) Extraoral photograph B) Intraoral photograph

Sequential appliances were delivered and replaced at 10-day intervals, corresponding to the programmed activation stages of the 4D NAM system.

Clinical assessment of hypersensitivity

Baseline evaluation

A comprehensive intraoral examination was performed prior to appliance insertion to confirm the absence of pre-existing mucosal lesions, erythema, or ulceration (Figure 2). The infant was also observed for presence of any type of cry and suckling reflex as an indicator of behavioural response.

Figure 2: Intraoral examination was performed prior to appliance insertion (first tray).

Follow-up evaluation (every 10 days)

Clinical assessments were carried out at each 10-day interval during subsequent tray changes. All examinations were performed by a single calibrated examiner to ensure consistency.

The oral mucosa was evaluated for blanching (localized ischemic whitening), erythema (mucosal redness), edema (soft tissue swelling), ulceration (loss of epithelial integrity). (Figure 3)

However, a grading system (Figure 4) was introduced to clinically evaluate the oral mucosal hypersensitivity in infants, where grade '0' suggests normal oral mucosa with intact epithelium, uniform pink colour, absence of redness, swelling, lesions or ulceration and grade '5' suggests presence of ulcer, necrotic patches, pseudomembranous slough, severe tissue destruction. Deep ulcers across multiple sites shows marked breakdown of tissue continuity.

All the 17 infants showed grade '0' during initial tray insertion and subsequent tray changes.

Figure 3: The oral mucosa was evaluated for blanching (localized ischemic whitening), erythema (mucosal redness), edema (soft tissue swelling), ulceration (loss of epithelial integrity) during subsequent tray changes a) After tray no 1, b) tray no 3, c) tray no 5.

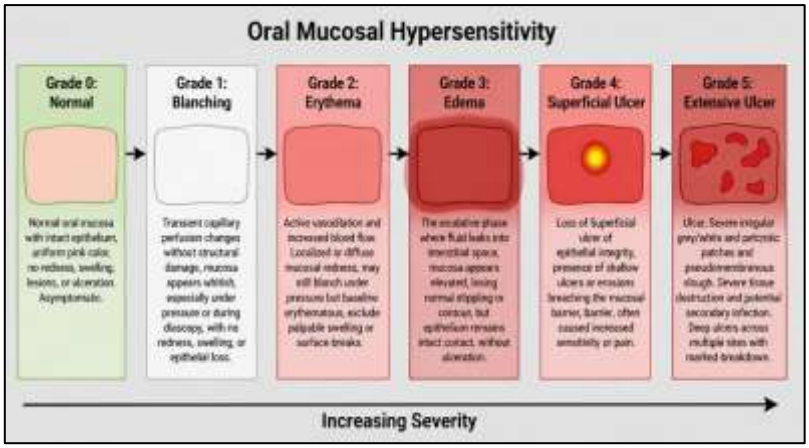

Figure 4: Grading criteria used for the clinical evaluation of oral mucosal hypersensitivity in infants

Presence or absence of Crying, feeding difficulty or refusal was checked every time while changing the tray by checking the positive suckling reflex. This parameter can be used as surrogate indicators of discomfort in infants.

RESULTS

17 infants with cleft lip and/or palate were included in the study and evaluated at regular 10-day intervals corresponding to sequential tray changes of the 4D NAM appliance. All participants completed the study without dropouts.

At baseline, the oral mucosa was clinically healthy in all infants, with no evidence of pre-existing lesions, erythema, or ulceration. Throughout the follow-up period, no intraoral clinical signs of hypersensitivity were observed. Specifically, there was no evidence of mucosal blanching, erythema, edema, or ulceration at any evaluation interval. The oral tissues remained stable and well adapted to the appliance across all visits.

All infants demonstrated good tolerance to the appliance. Positive suckling reflex was recorded in every tray changes. Feeding patterns remained normal, and no episodes of feeding difficulty or refusal were reported. There were no instances of persistent crying, irritability, or excessive salivation attributable to the appliance. Caregiver feedback indicated satisfactory acceptance and ease of use.

The clinical course was uneventful in all cases. No interruptions in treatment were required, and no emergency visits related to mucosal irritation or appliance intolerance were reported. The appliances exhibited adequate intraoral retention and adaptation throughout the study period.

Overall, none of the infants exhibited any clinical signs or symptoms suggestive of hypersensitivity to the 4D NAM appliance during the observation period.

DISCUSSION

The present prospective study evaluated intraoral clinical signs of hypersensitivity associated with 4D nasoalveolar molding (NAM) appliances fabricated using a thermo-responsive TA28 polymer in infants with cleft lip and palate. The principal finding of this investigation was the complete absence of clinical signs of hypersensitivity, including mucosal blanching, erythema, edema, and ulceration, throughout the observation period. In addition, no adverse behavioural responses such as feeding difficulty, irritability, or excessive crying were reported. These findings collectively indicate excellent intraoral tolerance and favourable biocompatibility of the 4D NAM appliance system.

Presurgical NAM therapy has become a cornerstone in the early management of cleft lip and palate, primarily due to its ability to reduce cleft width, align alveolar segments, and improve nasal form prior to surgical intervention.[11] However, conventional NAM appliances are associated with certain limitations, particularly related to tissue response. The need for frequent manual adjustments introduces variability in force magnitude and direction, which may lead to localized pressure concentration and subsequent mucosal irritation.[10] Clinical reports have documented complications such as erythema, ulceration, and soft tissue breakdown, often necessitating appliance modification or temporary discontinuation of therapy.[12] In contrast, the absence of such findings in the present study suggests that the 4D NAM system may overcome several of these inherent limitations.

A key factor contributing to the favourable tissue response observed in this study is the mode of force delivery associated with 4D appliances. Unlike conventional NAM, which relies on intermittent activation[10], 4D NAM appliances utilize thermo-responsive materials capable of delivering continuous, low-magnitude forces upon exposure to intraoral temperature. From a biomechanical perspective, light and continuous forces are known to be more physiologic, promoting gradual tissue adaptation while minimizing ischemic injury and inflammatory responses.[13] The absence of blanching, which is often an early indicator of excessive localized pressure, supports the notion that the forces generated by the 4D appliance remained within a biologically acceptable range.

In addition to force characteristics, the precision of appliance fabrication plays a critical role in determining tissue response. The integration of digital workflows, including three-dimensional scanning, planning of 4D NAM in

DAD software, and manufacturing through direct printing technology, allows to produce highly accurate and customized appliances. Improved adaptation of the appliance to the intraoral anatomy reduces the likelihood of pressure points and uneven force distribution. In the present study, the consistent absence of erythema and ulceration across all participants suggests that the combination of digital design and controlled material behaviour resulted in optimal load distribution and minimized tissue trauma.

Another important aspect of this study is the evaluation protocol, which was aligned with the clinical workflow of 4D NAM therapy. Assessments were performed at 10-day intervals corresponding to sequential tray changes, thereby capturing both immediate and cumulative tissue responses. This approach differs from conventional studies that often focus on short-term or post-adjustment observations. The absence of delayed hypersensitivity reactions in the present study indicates that prolonged exposure to the appliance does not adversely affect mucosal integrity, further supporting its safety for continuous intraoral use.

Vocalizations during cry are characterized by a sudden, high-amplitude onset followed by a prolonged, tense expiratory phase that often involves breath-holding.[14,15] This vocal profile exhibits elevated fundamental frequency and higher intensity levels compared to other distress states, reflecting an acute physiological stress response.[16] Furthermore, pain-elicited cries demonstrate significantly higher source instability, which effectively suppresses individual identity-specific acoustic markers in favour of urgent distress signaling.[17] By contrast, these discomfort-related vocalizations maintain a degree of spectral stability, allowing for the potential discrimination of behavioural states through an analysis of fundamental frequency and excitation source energy.[18] All the infants exhibited transient crying following insertion of the initial NAM appliance, likely reflecting initial adaptation to the intraoral device. However, persistent crying was not observed following insertion of subsequent appliances at 10-day intervals, indicating rapid adaptation to the therapy. All infants demonstrated good tolerance to the appliance.

Behavioural observations provide an additional dimension to the assessment of hypersensitivity in infants, who are unable to verbally communicate discomfort. In the present study, all infants demonstrated normal feeding patterns and did not exhibit signs of distress such as persistent crying or irritability. Feeding efficiency is a critical functional parameter in cleft patients, and any intraoral appliance that interferes with feeding may compromise overall treatment success.[19] The absence of feeding difficulties suggests that the 4D NAM appliance was well tolerated functionally and did not impede oral activity. These findings are consistent with the concept that improved appliance fit and controlled force application contribute to enhanced patient comfort.

The findings of this study are particularly relevant in the context of emerging 4D printing technology primarily focused on the mechanical properties, shape-memory behaviour, feasibility of TA 28, clinical evidence regarding their biological performance remains limited. The present study contributes to this evolving body of knowledge by providing in vivo data on soft tissue response in cleft infants. The absence of clinical hypersensitivity signs supports the biocompatibility of thermo-responsive TA 28 polymers used in 4D NAM appliances and highlights their potential for safe clinical application.

Conventional appliances are passive structures that require external adjustments to achieve desired outcomes, whereas 4D appliances are designed to adapt over time in response to environmental stimuli. This shift introduces the possibility of more personalized and biologically responsive treatment approaches. In the context of NAM therapy, such advancements may reduce the burden of frequent clinical visits, improve treatment efficiency, and enhance patient and caregiver compliance.[20]

Despite the favourable outcomes observed in this study, certain limitations must be acknowledged. The sample size was relatively small, which may limit the generalizability of the findings. Additionally, the absence of a control group treated with conventional NAM appliances precludes direct comparison of tissue response between the two modalities. The assessment of hypersensitivity was based on clinical and behavioural observations without the use of objective measures such as histological evaluation or biomarker analysis. Furthermore, the duration of follow-up was limited to the presurgical phase, and long-term tissue response beyond this period was not evaluated.

Future research should aim to address these limitations by incorporating larger sample sizes, randomized controlled designs, and longer follow-up periods. Comparative studies evaluating 4D NAM and conventional NAM would provide valuable insights into differences in tissue response, treatment efficiency, and clinical outcomes. In addition, the use of advanced diagnostic tools, such as digital pressure mapping or imaging-based tissue analysis, may enhance the understanding of biomechanical and biological interactions associated with 4D appliances.

Within the limitations of the present study, the findings demonstrate that 4D NAM appliances fabricated using thermo-responsive TA28 polymers are well tolerated in infants with cleft lip and palate. The absence of clinical signs of hypersensitivity, combined with favourable behavioural responses, suggests that these appliances provide a biologically compatible and clinically acceptable alternative to conventional NAM therapy.

CONCLUSION

Within the limitations of this study, 4D nasoalveolar molding appliances fabricated using a thermo-responsive TA28 polymer demonstrated excellent intraoral biocompatibility in infants with cleft lip and palate. No clinical signs of hypersensitivity, including mucosal blanching, erythema, edema, or ulceration, were observed at any stage of treatment. Although a brief episode of crying was observed following the initial insertion of the appliance,

this was transient, and infants adapted rapidly, with subsequent appliances being well tolerated. No persistent adverse behavioural responses or feeding difficulties were reported during treatment. These findings suggest that 4D NAM therapy provides a safe, well-tolerated, and clinically acceptable approach for presurgical orthopaedic management in infants with cleft lip and palate.

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