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Review

Protocols in the management of cleft lip and palate: A systematic review Running Title: Management of Cleft Lip and Palate

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ABSTRACT

Aim: To identify clinical decisions on surgical as well as non-surgical modalities for the treatment of CLP patients based on randomized controlled trials (RCTs).
Materials and methods: PubMed, Ebscohost, and Cochrane Library were searched and 20 articles based on RCTs conducted on cleft patient management were identified.
Results: The topics explored were infant orthopedics, lip and palate repair, alveolar bone grafting, and management of cleft maxillary hypoplasia. Nasoalveolar molding (NAM) was found to have great benefits when carried out within one month of birth. Fisher and Mohler's lip repair technique and use of recombinant human bone morphogenetic protein-2 (rh-BMP2) for alveolar bone grafting showed promising results. rh-BMP2 for alveolar bone grafting appears to be a promising alternative to autografts.
Conclusion: Early commencement of NAM in neonatal life is of great benefit to cleft patients. There is a need for more multicentre collaborations, mainly to identify the ideal surgical technique to reduce the variability in treatment and to ensure that the patient receives appropriate evidence-based treatment.

1. Introduction

Orofacial cleft (OC) is the non-fusion of the facial structures between the 5th and 10th week of gestation [1]. During the fourth and eighth weeks of embryonic development, failure in the fusion of the frontonasal and maxillary processes leads to the formation of a cleft lip [2]. This can lead to abnormal positioning of the tongue and often affect palatal development. The worldwide prevalence of OCs is about 1 per 500 to 700 live births (WHO 2012). Hence, OCs are considered one of the most common congenital anomalies. It is more frequent in Asians and Native Americans and boys (60% to 80%) (WHO 2004). A cleft lip is associated with a cleft palate in 68% to 86% of cases [3]. Genetic predisposition, environmental factors, and teratogenic agents (for example maternal smoking, zinc and folate deficiency, alcohol, pesticides, chemical solvents, antiepileptic drugs, etc.) are considered as potential risk factors [4].

The approach towards the management of cleft lip and palate (CLP) is multidisciplinary, and the cleft team should consist of craniofacial surgeons, otolaryngologists, geneticists, anaesthesiologists, speech-language pathologists, nutritionists, orthodontists, prosthodontists, and psychologists, neurosurgeons and ophthalmologists. To provide long-term follow-up through the entire child's development and achieve all the treatment goals such as normalized facial aesthetic, proper feeding in neonatal life, the integrity of the primary and secondary palate, normal speech and hearing, airway patency, class I occlusion with normal masticatory function, good dental and periodontal health, normal psychosocial development and good quality of life [5].

There is no standardized management of CLP that is accepted currently by all cleft centers; there is a striking diversity of clinical practice in the area. Evidence-based medicine should be the answer to the uncertainties in the treatment; however, there is a paucity of the high level of evidence (i.e., systematic reviews and randomized controlled trials on CLP. Hence, many clinical decisions are made based on biased evidence from sporadic case reports or retrospective studies. The questions commonly pondered upon by clinicians can only be rightly answered by sound scientific data from clinical trials.

The present systematic review was conducted to find clinical decisions on surgical as well as non-surgical modalities of cleft treatment based on randomized controlled trials (RCTs). Our review had an objective to evaluate the timings of various surgical modalities in the treatment of unilateral/bilateral CLP based on the chronologic age of the patients. We also assessed the outcomes of various surgical modalities in terms of improved facial aesthetics, feeding, velopharyngeal function, speech and hearing, maxillary growth stability, psychosocial development, and quality of life following the management of CLP.

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2. Materials and methods

The review protocol was registered on the PROSPERO database with registration ID: CRD42021224955. Searches for RCTs were made in three databases (Cochrane Library, Ebscohost, and PubMed) conducted from December 2010 – December 2020 on Non-syndromic children with congenital anomalies of CLP. In the Pubmed database, we used search strategies involving the MeSH descriptors, Boolean logic operators, and free-text truncated with an asterisk. The main descriptors used were

i "Surgical Procedures, Operative"[Mesh] OR “Surgical treatment” OR “Surgical Treatment Modalities”
ii “Unilateral Cleft Lip” OR “Cleft Lip Repair” OR "Cleft Lip"[Mesh] OR “Cleft Lip Surgery” OR “Harelip”
iii “Unilateral Palate” OR "Cleft Palate"[Mesh] OR “Primary palatoplasty” OR “Cleft Palate Surgery”
iv "Infant"[Mesh] OR "Child, Preschool"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]

The phrase “Surgical Modalities in management of Cleft lip palate” was used to search in the other two databases. The overall process of inclusion and exclusion of articles in our systematic review is depicted in Fig. 1.

The risk of bias in the results of each study contributing to an estimate of effect was assessed by means of the Cochrane risk of bias assessment tool. (attached as supplementary material)

3. Result

The issues discussed by the 20 selected articles were as follows:

i Infant orthopaedics (Nasoalveolar moulding): 6/20 = 30%;
ii Lip and palate repair procedures: 6/20 = 30%;
iii Management of the cleft maxillary hypoplasia: 3/20 = 15%;
iv Alveolar bone grafting with bone grafts: 5/20 = 25%.

The data extracted from all the articles is presented in Table 1 and their conclusions are summarized in Table 2, where the signs “<,” “>,” “*”, and “=” mean, respectively, that the experimental approach is “less recommended than,” “more recommended than,” “Inconclusive” and “equivalent to” control.

4. Discussion

CLP patients suffer from functional and aesthetic problems and as a result, have to undergo multiple procedures throughout their lifetime. There are multiple surgical and non-surgical treatment modalities like presurgical orthopedics, correction of cleft lip, nose, and palate deformity, scar revision surgery, alveolar bone grafting, orthognathic surgery, distraction osteogenesis, and rhinoplasty.

Each of the procedures has been associated with controversies regarding the timing and the best possible method of surgeries to be performed. The clinician is therefore presented with various options and must choose wisely to provide the best possible treatment for the patient. In this systematic review, we attempted to obtain

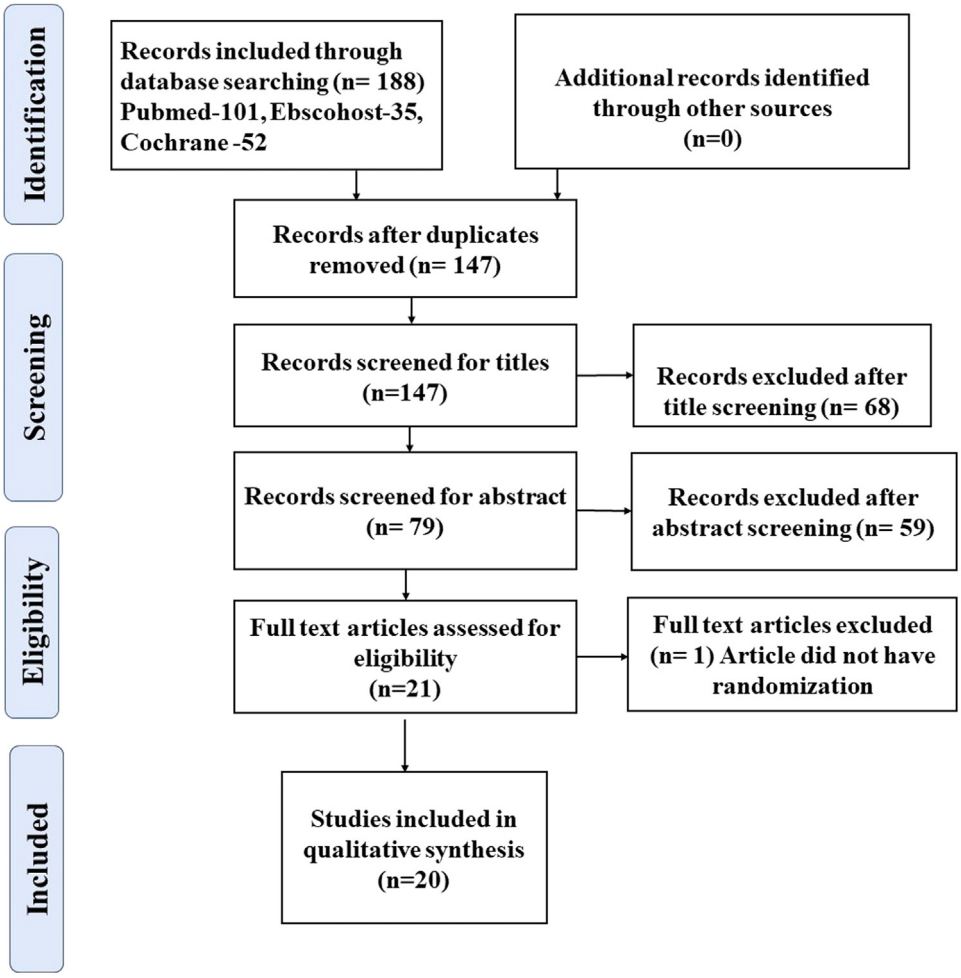

Fig. 1. PRISMA flow diagram depicting selection and exclusion of the studies in the review process

Table 1
Summarization of extracted data from the articles included in the systematic review.

AUTHOR	YEAR OF STUDY	NO. OF PATIENTS ENROLLED IN THE STUDY	CHRONOLOGIC AGE OF THE PATIENTS	TYPE OF CLEFT TREATED	EXPERIMENTAL GROUP	CONTROL GROUP	OUTCOME
PRESURGICAL ORTHOPAEDICS							
Jahanbin et al	2020	20	Newborn infant	UCLP	Addition of nasal stent to NAM plate	Addition of nasal stent to NAM plate when alveolar gap reached 5 mm	Columellar angle, nostril width on the cleft side, nostril height on the cleft side, soft tissue cleft width, and nasal surface area
Mohamed Abd El-Ghafour et al	2020	34	Infant	UCLP	3D-printed Nasoalveolar moulding (D-NAM)	Without Nasoalveolar moulding	Improvement in the maxillary arch dimension
Saad et al	2020	40	Infant	UCLP	Nasoalveolar moulding	Without Nasoalveolar moulding	Amount and rate of cleft gap changes, the midline position, and the transverse, sagittal, and vertical growth
Shetty et al	2015	150	1 month-8 months	UCLP	Group 1: NAM performed at 1-6 months of age Group 2: NAM performed at 6 months- 1 yr of age Group	NAM performed by 1 month of age	Improvement in intersegment distance, nasal height, nasal dome height, and columella height
Shetty et al	2011	30	1 month-5 months	UCLP	Group 1: NAM performed with 1 months of age Group 2: NAM performed at 1-5 months of age	Non- cleft patients	Improvement in intersegment distance, nasal height, nasal dome height, and columella height
TYPE AND TIMING OF LIP REPAIR							
Mazin Deshmukh et al	2018	50	8.5 months	CLP with or without palate	Fischer technique	Mohler technique	Improved aesthetic
TYPE AND TIMING OF PALATOPLASTY PROCEDURE							
Antonelli et al	2011	673	At 9-12 months or 15 to 18 months of age	UCLP	Von Langenbeck with intravelar veloplasty	Furlow palate repair	Hearing & otoscopic findings at 5-6 years age
Williams et al	2011	467	At 9-12 months or 15 to 18 months of age	UCLP	Von Langenbeck with intravelar veloplasty	Furlow palate repair	Velopharyngeal function Occurrence of palatal fistula
Ganesh et al	2015	85	Mean age of lip and palate repair for VF group 5.52 and 12.3 months. And for TF group 6.3 and 12.9 months	UCLP	Vomer flap (VF)	Two flap (TF) technique	Evaluation of dental arch relationship
SECONDARY BONE GRAFTING							
Alonso et al	2010	16	8-12 years	UCLP	RhBMP-2	Illiac crest autogenous bone graft	65% bone height gain in experimental group as compared to 83.8% in control group
Canon et al	2012	12	8-15 years	UCLP	RhBMP-2	Illiac crest autogenous bone graft	
Gomes et al	2012	48	23-26 years	UCLP BCLP	Bone grafts filled in gaps created by Le Fort osteotomy	Le Fort I osteotomy without bone grafts	Increased post-operative stability
Takemaru et al	2015	15		UCLP	Composite graft of iliac crest with HA (COL)	Illiac crest autogenous bone graft	
Chang et al	2016	24	9years	UCLP	Pre-orthodontic treatment followed by SABG	SABG without pre-orthodontic treatment	Improved bone graft volume and central incisor position
MANAGEMENT OF CLEFT MAXILLARY HYPOPLASIA							
Chua et al	2010	42	16years	Not mentioned	Distraction osteogenesis	Conventional Le Fort osteotomy	Long term stability
Chua et al	2012	42	16years	Not mentioned	Distraction osteogenesis	Conventional Le Fort osteotomy	Speech and velopharyneal changes, soft tissue profile, psychologic profile
Hongbo et al	2012	10	19.2 years	6- UCLP 3- BCLP 1-CP	Anterior segmental Distraction osteogenesis	Distraction osteogenesis	Velopharyngeal closure function, Hypernasality, nasalance

Table 2
Conclusions drawn after review of articles pertaining to various aspects of the management of patients with cleft lip and palate.

Conclusion from articles on	Experimental group	Conclusion	Control	Remarks
Presurgical infant orthopedics	Patients who had Nasoalveolar molding	>	Patients who did not have Nasoalveolar molding	Effective, improves aesthetics and nasal symmetry
Alveolar bone grafting	Cleft repair with rhBMP-2	=	Iliac crest bone graft	Increased bone regeneration & lower patient morbidity Prevents donor site morbidity
Cleft Maxillary hypoplasia	Distraction Osteogenesis	=	Conventional orthognathic surgery	No statistically significant difference velopharyngeal insufficiency
	Distraction Osteogenesis	>	Conventional orthognathic surgery	Increased long term stability
	Anterior segmental distraction osteogenesis	>	Osteogenesis distraction	Improved velopharyngeal function
Lip and Palate repair	Fischer's technique of lip repair	>	Mohler technique of lip repair	—
	Spina technique for lip repair and Von Langenbeck with intravelar veloplasty for palatal repair	=/*	Millard technique for lip repair and Furlow palate repair	
	vomer flap (VF), whereby patients underwent primary lip nose repair and vomer flap for hard palate single-layer closure, followed by soft palate repair 6 months later	*	Two-flap technique (TF)	
	One stage palatoplasty	*	Two-stage palatoplasty	

information regarding the best time to carry out all the procedures and the ideal surgical procedure to carry out the same by searching for RCTs that address these issues.

Presurgical infant orthopedics (PSIOs) is one of the first steps performed in cleft lip cleft palate patients. It includes an alveolar lip strap, alveolar molding, NAM, and lip adhesion. Nasoalveolar molding is done to mold the perioral structures by bringing the nasolabial and maxillary segments together. This procedure takes the advantage of high quantities of hyaluronic acid in newborns which renders increased tissue elasticity [6]. It can reduce the volume of the defect, correct alignment of the maxillary segment and palatal shelves, helps in feeding, improve nasal symmetry, and simplify the surgical repair of cleft lip, palate, and nose. Whereas, the disadvantages include high cost, need for parental cooperation, and restriction of maxillary growth.

PSIOs encompass a wide range of appliances that are used for different durations and can produce different results that cannot be generalized. Multiple studies have shown that it can reduce the cleft gap but its adverse effects on maxillary growth are still unclear [7].

In all six studies in this review found, a statistically significant reduction in cleft gap and improvement in nasal symmetry with NAM.[8–10] The average age of the study population was less than 1 month in all the studies except for Shetty et al who included a second group with ages varying from 1-5 months. Best results were seen when NAM was carried out less than 1 month of age but effects are evident even when done up to 5 months of age albeit less significant. One study compared the Modified Figueroa and Grayson's technique and found that the latter was more efficient in reducing nasal width but had higher chances of developing of ulcers [11]. Saad et al found that those not treated with NAM showed a slight increase in cleft gap [12].

Shetty et al found that improvements in horizontal and vertical measurements at the end of NAM were maintained up to 18 months of age and found no negative impact on maxillary growth. They followed up with these patients at 6 years of age and found that the group that did not undergo NAM had a higher risk of collapse of the anterior segment. This suggests that NAM can prevent the collapse of the arch [13]. Our review emphasizes the inclusion of NAM as an important technique in the comprehensive management of cleft patients within 0- 3 months.

Cleft lip repair techniques focused on restoring lip continuity, establishing the symmetry of the cupid's bow and the nose, and repairing the defective orbicularis oris muscle. Lip repair performed as early as immediately post birth within 3 months of age. Early repair produces the best results but carries with it the inherent risks associated with putting a newborn under general anaesthesia [14].

A common rule that has been around for the last 60 years approximately is the "rule of 10s" first proposed by Wilhelmsen and Musgrave in 1966 and modified by Millard in 1976. Although quoted quite often there wasn't sufficient evidence to support the postponement of surgery till the child attains 10 pounds weight, 10gm/dl hemoglobin, and a WBC count of fewer than 10,000 cells per cubic microlitre. Millard introduced the 10-week rule where he stated that surgery can be performed post the 10-week mark in addition to the weight and haemoglobin [15]. The primary aim of the rule of ten was to avoid the complications associated with general anesthesia. Chow et al in 2016 found that only the weight of the patient affected the incidence of complications and that the other factors did not play a major role as previously assumed [16]. Hammoudeh et al had good results when the cleft repair was carried out as early as 34 days postbirth and had a low complication rate (6%) [17].

In the early 200s, Millard's technique or versions of it was the most commonly used as reported by Sitzman et al [18]. Nowadays, surgeons are increasingly repairing the nasal floor at the time of cleft lip repair. The rotation and advancement technique for lip repair is the most common technique used nowadays with Mohlers and Noordoff's modifications being popularly followed by the more recently introduced Fisher anatomic subunit technique [19].

Deshmukh et al compared Fischer and Mohler's technique for cleft lip repair and found the former produces better aesthetic outcomes [20]. There were no RCTs assessing primary cleft rhinoplasty techniques. One paper addressed secondary cleft rhinoplasty in 60 patients in the setting of cleft nasal tip and found that the addition of a graft from the lower lateral cartilages improves tip projection [21].

Cleft palate repair is usually performed nine months after the cleft lip repair. It can be done in a single stage or two stages. Delayed repair of the soft palate can impair speech development whereas early repair of the hard palate can cause excessive restriction of maxillary growth. To overcome this, a two-stage palate repair was proposed where the soft palate is repaired early to allow normal speech development, and hard palate repair is delayed to minimize the negative impact on the growth of the maxilla caused by the stripping of the periosteum involved in hard palate repair. Reddy et al compared outcomes of single-stage versus two-stage palatoplasty in 100 patients and concluded that there was no difference in terms of fistula formation and hypernasality [22].

Two studies compared Furlow with von Langenbeck intravelar veloplasty techniques.[23,24] with study samples of 673 and 370, the

Table 3
Proposed protocol for the management of cleft lip and palate.

Timing	Procedure
After 16 weeks of pregnancy	Cleft lip diagnosis using Ultrasound.
Prenatal	Discussion & consultation with a geneticist and craniofacial surgeon.
0- 3 months	Pre-surgical Naso-alveolar molding
3-6 months	Primary Lip and Nose repair once 10 pounds of weight is attained. Techniques: Mohler/Fischer/Nordoff / miller
9-18 months	Soft and Hard Palate repair Techniques: Von-Langenbeck's with intravelar veloplasty/Furlow/Vomer flap/Two flap technique
5Years	Intermediate Rhinoplasty / Lip Revision- superficial defects
8-12 years	Secondary bone grafting with Iliac crest bone autograft/rhBMP2
16 years and above	Distraction Osteogenesis/Anterior Segmental distraction Osteogenesis/Orthognathic Surgery with grafting if needed/Combination of Distraction Osteogenesis and Orthognathic Surgery Secondary Rhinoplasty Correction of muscle-related residual deformities of lip

largest of any literature available on the surgical techniques with a 4-year follow-up. These studies found the Furlow technique was associated with improved velopharyngeal function but a higher incidence of fistula formation and cited equivalent otologic and audiological outcomes for the 2 repair styles [25]. Another study found that palatal repair with a Vomer flap (VF) produced better growth outcomes but speech outcomes were better with Two flaps (TF) [26]. There is no single technique that produces limited restriction of maxillary growth while also allowing for normal speech development.

Alveolar bone grafting (ABG) is performed to close the oronasal communication, improve ala symmetry, restore the continuity of the alveolus, and aid in the eruption of the permanent lateral and canine. The ideal time for this procedure has been a topic of debate for years. Early grafting is done in the deciduous dentition stage, secondary grafting in the mixed dentition stage, and tertiary in the permanent dentition stage [27]. An SRMA by Rajae et al concluded that the optimal timing of ABG that provides the best results is between 8 and 12 years, before or just after the eruption of permanent canines adjacent to the cleft [28]. In all the included studies the procedure was performed at 9-12 years of age. Chang et al found that presurgical orthodontics improves the bone fill after ABG [29].

Autogenous, allogenous, or alloplastic materials have been tried to graft the cleft alveolus. Cortical or cancellous autogenous bone from the cranium, iliac crest, mandibular symphysis, tibia, rib, and femur has been tried. The iliac crest is one of the most preferred options as it can provide a huge quantity of cancellous bone and is relatively easy to harvest. However, it may need hospitalization for a few days, causing a temporary change in gait [30]. Iliac crest in combination with HA has been tried to reduce the quantity of autogenous bone needed. An alternative for iliac crest graft that has gained popularity in recent years is the rhBMP-2, an option that will eliminate morbidity related to a second surgical site. ABG was one of the most commonly studied topics in current literature.

A study by Alonso et al showed that 65% of bone height could be achieved with rh-BMP2 [31]. rhBMP-2 was radiographically and clinically successful in regenerating the bone at the alveolar cleft which resulted in a shortening of the operation time, absence of donor site morbidity, and a shorter hospital stay. Two RCTs that compared rh-BMP2 with iliac crest graft found that the former was capable of providing good quality and quantity of bony regeneration in the cleft. Due to the small sample size of the studies and lack of long-term follow up we cannot assure the safety of its theoretical risks.

Once growth and development are completed, the focus shifts to correcting the midfacial deficiency. Until the last half of the 20th century, Le Fort I osteotomy was the procedure of choice to treat midfacial hypoplasia in patients with CLCP. In recent years, distraction osteogenesis (DO) has gained popularity in treating maxillary hypoplasia to overcome the high rates of relapse (20-25%) and adverse effects on velopharyngeal function associated with Le fort 1 surgery. DO allows slow stretching of the muscles and soft tissue histogenesis which does not take place in conventional orthognathic surgery [32]. Distraction requires two surgeries under general anesthesia that can substantially increase the cost and is also hugely dependent on patient cooperation for its success.

According to the literature review by Scollozi et al, advancements greater than 6mm require DO whereas Chua et al thought that there was no difference in terms of speech outcomes up to 10mm advancement with either technique [33]. However, a meta-analysis by Cheung et al concluded no statistical significance between the type of procedure and surgical relapse, velopharyngeal function, hyper nasality, and speech when advancement was between 6-10mm [34].

In this review, one paper focused on conventional Le Fort I advancement compared with distraction osteogenesis, and DO was found to provide improved horizontal and vertical skeletal stability over time. In terms of speech, however, there was no difference suggesting that DO does not provide an extra advantage over Le fort in preventing Velopharyngeal insufficiency (VPI) for 6-10mm advancement [35]. Chua et al also analyzed the psychological impact of le fort1 and DO and found that both had a positive impact on patients and reduced distress up to two years post-procedure [36]. Gomes et al found that relapse in Le fort 1 advancement can be reduced by grafting the gaps to enhance stability [37].

A modification of conventional distraction osteogenesis is Anterior Segmental Distraction Osteogenesis (ADO) which aims to prevent the worsening of VPI and reduce the complications associated with conventional DO. Yu et al found that ADO is superior in preventing the worsening of VPI and hypernasality. It is a promising and valuable technique that requires further exploration [38].

The paucity of RCTs on cleft patient management has made it difficult to conclude the ideal timing and ideal techniques for the different procedures used to treat the cleft patient. Various techniques have been tried over the years and the tools used to measure the outcomes varied drastically between the studies as well. The majority of the studies available also had a short duration of follow up and as any cleft treatment has a long-term impact, it is difficult to conclude which is the best treatment modality without having information on long-term effects. There is a need for more well-designed multicentre RCTs but according to the few RCTs and literature available, we formed a protocol of clinical decisions about the time frame and a few surgeries. (Table 3)

5. Conclusion

Few evidence-based RCTS regarding Cleft treatment are available in the literature. In the present systematic review, it is clear that NAM is beneficial when carried out within a few months of birth.

There is no consensus on which technique of lip repair is best, but Fischer and Mohler's techniques of lip repair are being increasingly utilized. Also, with the development of technology, surgeons can take up cleft surgeries just a few days after birth. The best technique for cleft palate repair is also unanswered. Rh-BMP2 is emerging as a suitable alternative to iliac crest graft for ABG albeit with inadequate evidence. Distraction osteogenesis and ADO appear to be slightly superior in treating maxillary hypoplasia but more studies are needed to establish this fact. No RCTs that answered questions about the ideal timing of these surgeries were identified. The time frame developed from our review would serve to guide the surgeons in clinical decision-making.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare

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