Original Article

pISSN, eISSN 0125-5614
M Dent J 2023; 43 (1) : 9-20

Long-term effect of nasoalveolar molding on skeletal and dental development in patients with oral clefts; a systematic review and meta-analysis

Ard Likitkulthanaporn[1], Supatchai Boonpratham[2], Yanasinee Honglertnapakul[1], Nuntinee Nanthavanich Saengfai[2], Chaiyapol Chaweewannakorn[2], **Supakit Peanchitlertkajorn**[2]

[1] *Residency Training Program in Orthodontics, Faculty of Dentistry, Mahidol University, Bangkok, Thailand*
[2] *Department of Orthodontics, Faculty of Dentistry, Mahidol University, Bangkok, Thailand*

Objective: This study aimed to analyze the treatment effects of pre-surgical nasoalveolar molding (PNAM) on cephalometric characteristics and dentoalveolar outcome for patients with non-syndromic unilateral cleft lip and palate by conducting a systematic review and meta-analysis.
Materials and Methods: Five electronic databases and two journals were searched up through October 2021. Studies comparing treatment results between PNAM and non-PNAM treatment protocols were selected for analyses. Cephalometric characteristics and dentoalveolar outcome were outcomes of interest. Data extraction, methodological quality assessment, risk of bias assessment, and meta-analysis were performed.
Results: Four retrospective cohort studies were selected for a qualitative review and meta-analysis. The risk of bias assessment was moderate for all studies. Treatment results from patients who underwent PNAM were not significantly different from other treatment protocols.
Conclusion: This study found that PNAM does not improve cephalometric characteristics and dentoalveolar outcomes.
Registration: PROSPERO (CRD4202128384).

Keywords: cephalometric characteristics, cleft lip and palate, dentoalveolar outcome, nasoalveolar molding

How to cite: Likitkulthanaporn A, Boonpratham S., Honglertnapakul Y, Nanthavanich Saengfai N, Chaweewannakorn C, **Peanchitlertkajorn S.** Long-term effect of nasoalveolar molding on skeletal and dental development in patients with oral clefts; a systematic review and meta-analysis. M Dent J 2023;43(1):9-20.

Introduction

Pre-surgical nasoalveolar molding (PNAM) is a type of cleft infant orthopedic treatment (CIOT) [1]. Its goal is to improve the nasolabial esthetic outcome of patients with oral clefts. It was first reported by Grayson *et al* in 1993 [2]. PNAM is different from other types of CIOT because of an addition of a nasal stent to the labial flange of an oral plate. PNAM enhances nasal outcomes by pre-surgically improving the shape of lower lateral nasal cartilage, nasal tip projection, and elongating columella [3, 4]. At the time of birth, infants received a large amount of estrogen from their mothers, which results in increased hyaluronic acid production. When combined with cartilage proteoglycan, hyaluronic acid acts by breaking up the intercellular matrix, giving elasticity to cartilage, ligaments, and connective tissues. This is to enable the fetus to pass through the birth canal safely. The estrogen level begins to decrease about six weeks after birth. Therefore, nasal cartilage remains moldable during the first 3 months of life [5].

Corresponding author: Supakit Peanchitlertkajorn
Department of Orthodontics, Faculty of Dentistry, Mahidol University
6, Yothi Road, Ratchathewi, Bangkok 10400, Thailand
Tel: +662 200 7813-14 Fax: +662 200 7812
E-mail: supakitpeanc@gmail.com
Received: 10 March 2023 **Revised:** 3 April 2023 **Accepted:** 5 April 2023

Early PNAM articles were case series reporting mostly post-treatment results [1, 6, 7]. Some studies later reported a significant decrease in cleft size and improvement in nasal features [8-10]. A recent systematic review studied the effects of PNAM on patients with unilateral cleft lip with or without palate (UCLP) [11]. The authors concluded that PNAM significantly enhanced nasal symmetry, lengthened columella, as well as decreased alveolar cleft width before cheiloplasty. Another systematic review studied the long-term effects of PNAM on the nasal esthetics [12]. Although the long-term trend showed better nasal outcomes, researchers found discrepancies among the results of selected studies. And the evidence was limited. Meta-analysis was not conducted because different methodologies were used. Alfonso *et al* performed a systematic review to assess the burden of care related to the PNAM [13]. The physical burden such as treatment visits was compensated by psychosocial advantages. The additional cost of PNAM was offset by the diminished need for surgical revision. This is the first systematic review of NAM that included multiple randomized controlled trials (RCTs). However, the heterogeneity of the selected studies is too high to perform a meta-analysis.

Past systematic reviews emphasized mostly on nasal esthetics [11, 12]. Cephalometric characteristics and dentoalveolar outcomes are also very important clinical outcomes. But they have not been studied as much. Therefore, the goal of this study is to conduct a systematic review and meta-analysis to assess the long-term effects of PNAM on cephalometric characteristics and dentoalveolar outcomes for patients with non-syndromic UCLP.

Materials and Methods

The PRISMA-P recommendation was used as a guideline to conduct and report this systematic review [14]. The study protocol was registered a priori with PROSPERO (ID CRD4202128384).

All human studies were included in the literature search. Non-randomized-controlled trials (RCT) were included in this review due to a scarcity of RCTs on the subject. PICO was used to construct this systematic review with no language exclusion. The PICO is outlined as follows:

Patient:	Patients with UCLP aged 4 years old or older at the time of follow-up evaluation prior to receiving any orthodontic treatment and secondary alveolar bone graft (ABG)
Intervention:	Pre-surgical nasoalveolar molding (PNAM)
Comparison:	Treatment protocols without any form of cleft infant orthopedics treatment (No-CIOT), Treatment protocols that included a non-NAM cleft infant orthopedics treatment (Other-CIOT)
Outcome:	Cephalometric characteristics and Dentoalveolar outcome

In-vitro studies, animal studies, case reports/series, review articles, non-comparative studies, studies with a small sample size (< 10 per cohort), studies with syndromic patients, and studies with ineligible outcomes were excluded.

Search and selection strategy

Two reviewers (AL and YH) conducted a search of six electronic databases (Pubmed, Web of Science, Cochrane, Scopus, Embase, and Grey Literature) through October 2021. The search terms were: “Cleft patient” or

MeSH terms “Cleft lip” or “Cleft lip” or MeSH terms “Cleft palate” or “Cleft palate” or “Cleft lip and cleft palate” or “Cleft lip and palate” or “Alveolar cleft” or “CL” or “CLP” or “CL & CP” or “UCL” or “UCLP” or “UCL & P” or “Unilateral cleft lip” or “Unilateral cleft lip and palate” or “Unilateral cleft lip and cleft palate” or “Cleft lip with cleft palate”; and “Alveolar molding” or “Alveolar moulding” or “Nasoalveolar molding” or “Nasoalveolar moulding” or “Naso alveolar molding” or “Naso alveolar moulding” or “NAM” or “Presurgical nasoalveolar molding” or “Presurgical nasoalveolar moulding” or “PNAM” or “Presurgical nasal molding” or “Nasal molding” or “Nasal moulding”.

“Cleft Palate-Craniofacial Journal”, and “Plastic and Reconstructive Surgery Journal” were also manually searched. Secondary references from lists of review articles and meta-analysis were also examined for possible inclusion.

After duplicate removal, the same reviewers screened article titles and abstracts independently for eligible studies. Next, the full text of potential studies was reviewed for eligibility. Any disagreement on study inclusion or exclusion was determined by a consultation with the third reviewer (SP).

Data extraction and methodological quality assessment

The data were extracted independently using a standardized form by the same reviewers. The following data were extracted: 1) outcome assessment, 2) authors, 3) year of publication, 4) study design, 5) sample size, 6) age at follow-up, 7) type of PSIO performed, 8) inclusion of primary rhinoplasty in NAM protocols, 9) NAM starting age, 10) cheiloplasty technique performed in NAM group, 11) result, and 12) level of evidence. Corresponding authors were contacted for clarification as needed. Selected articles were also assessed for methodological quality according to “The Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCBEM)” [15].

The same reviewers independently performed the risk of bias assessment. Non-RCTs were assessed with ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) [16]. For ROBINS-I, each study was examined in seven domains: 1) confounding bias, 2) selection of participants into the study, 3) classification of interventions, 4) deviation from intended interventions, 5) missing data, 6) measurement of outcomes, 7) selection of reported result. The risk of bias for each domain and the overall bias can be classified as: “low” (if all domains were at low risk of bias); “moderate”, “serious”, “critical”, and “no information” (if one or more domains were rated as such).

Statistical analysis

Meta-analysis was performed using RevMan version 5 (The Cochrane Collaboration, Oxford, UK). The heterogeneity across studies was assessed using Cochran’s Q tests and I2 statistics and presented as forest plots [17]. The statistical significance level was set at $p < 0.05$. Low heterogeneity (P value > 0.10, I2 < 50%) indicates that a fixed-effect model should be employed whereas significant heterogeneity (P value < 0.10, I2 > 50%) requires a random-effect model. Publication bias was assessed by a visual inspection of funnel plots [18] and a linear regression-based Egger’s test. When asymmetry in the funnel plot was detected, Egger's test was used to determine statistical significance ($p < 0.05$) [19].

Results

An electronic database search yielded 1,003 records. The manual search added six more. 924 articles remained after duplicate removal. After title and abstract screening, 888 articles were excluded. Full texts of the remaining 36 studies were further examined. Additional 32 studies were removed for reasons described in Figure 1. A total of 4 articles were selected for qualitative meta-analysis (Figure 1). All of the selected studies are retrospective. Table 1 shows the characteristics of the selected studies and the level of evidence according to the OCEBM. Table 2 shows the number of participants, average follow-up age for each group of the treatment protocol, and assessed outcomes.

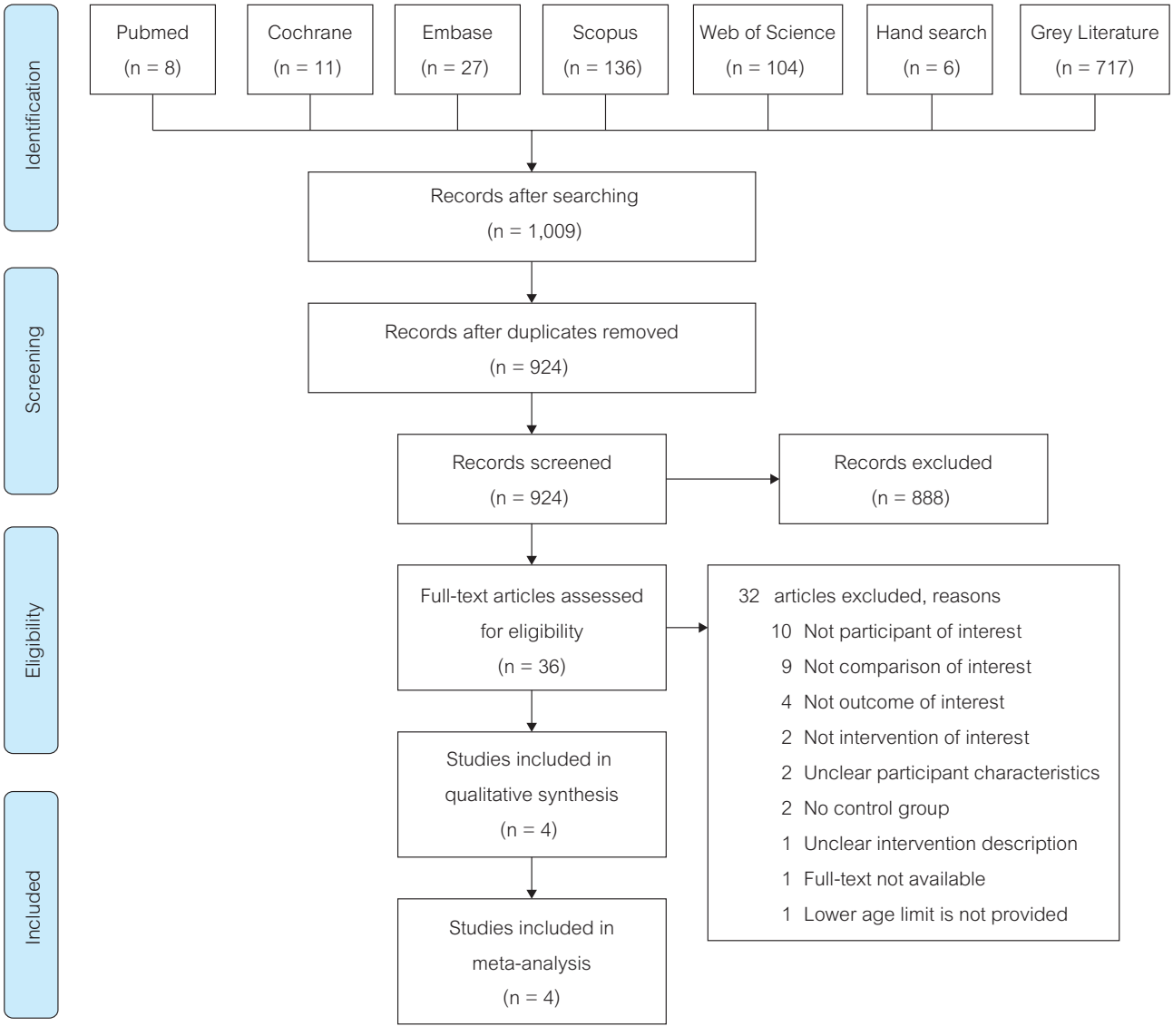


Figure 1 PRISMA flow diagram of the selection process

Table 1 Detailed characteristics of the included studies and level of evidence

Outcome assessment	Authors	Year	Study design	Sample size	Age at follow-up (Year)	Type of CIOT performed	Racial distribution	Primary rhinoplasty performed in NAM group?	NAM Starting age	Cheiloplasty technique performed in NAM group	Result	Level of Evidence
Cephalometric characteristics	Kornbluth *et al* [20]	2018	Retrospective cohort study	Group 1: 40 Group 2: 30 Group 3: 18 Group 4a: 17 Group 4b: 19	8.8	Group 1: No-CIOT Groups 2 & 3: Latham appliance Group 4a: PNAM Group 4b: Modified McNeil	Caucasian	N	NR	Anatomic Subunit Repair at 4-5 months	No-CIOT group showed the most favorable outcomes in terms of craniofacial characteristics.	2b
	Akarsu-Guven *et al* [21]	2018	Retrospective cohort study	Group 1: 26 Group 2: 20	5.1	Group 1: PNAM Group 2: No-CIOT	NR	N	1-2 weeks	Modified Millard at 3 - 4 months	No significant differences in craniofacial morphology between patients treated with and without PNAM.	2b
	Peanchitlertkajorn *et al* [22]	2018	Retrospective cohort study	Group 1: 39 Group 2: 40 Group 3: 37 Group 4: 32 Group 5: 34	8.1	Group 1: Molding plate Group 2: No-CIOT Group 3: Extraoral taping Group 4: Modified McNeil Group 5: PNAM	Caucasian, Hispanic	Y	2 weeks	Modified Millard at 3-5 months	No-CIOT group showed the most favorable outcomes in terms of craniofacial morphology.	2b
	Rubin *et al* [23]	2019	Retrospective cohort study	Group 1: 56 Group 2: 56	8.6	Group 1: PNAM Group 2: No-CIOT	Caucasian	Y	NR	Modification rotation advancement at 3 to 4 months	No significant differences in craniofacial morphology between patients treated with and without PNAM.	2b
Dentoalveolar outcome	Kornbluth *et al* [20]	2018	Retrospective cohort study	Group 1: 40 Group 2: 17 Group 3: 19 Group 4a: 28 Group 4b: 36	7.8	Group 1: No-CIOT Groups 2 & 3: Latham appliance Group 4a: PNAM Group 4b: Modified McNeil	Caucasian	N	NR	Anatomic Subunit Repair at 4-5 months	No CIOT group showed the most favorable dental arch relationship.	2b
	Peanchitlertkajorn *et al* [22]	2018	Retrospective cohort study	Group 1: 39 Group 2: 40 Group 3: 35 Group 4: 34	8.1	Group 1: Molding plate Group 2: No-CIOT Group 3: Modified McNeil Group 4: PNAM	Caucasian, Hispanic	Y	2 weeks	Modified Millard at 3-5 months	No CIOT group showed the most favorable dental arch relationship.	2b

Y denotes Yes; N, No; and NR, Not reported

Table 2 Number of participants and average follow-up age for each group of treatment protocol and assessed outcomes.

		Number of subjects			Average age at follow-up (year : month)		
		PNAM	No-CIOT	Other-CIOT	PNAM	No-CIOT	Other-CIOT
Cephalometric characteristics	Kornbluth *et al* [20]	17	40	67	8.8	9.5	8.7
	Akarsu-Guven *et al* [21]	26	20	-	5.1	5.1	-
	Peanchitlertkajorn *et al* [22]	34	40	108	8.1	8.1	9.0
	Rubin *et al* [23]	56	56	-	8.6	9.7	-
Dentoalveolar outcome	Kornbluth *et al* [20]	28	38	72	7.8	8.7	9.5
	Peanchitlertkajorn *et al* [22]	34	40	74	8.1	8.1	8.6

Risk of bias within studies

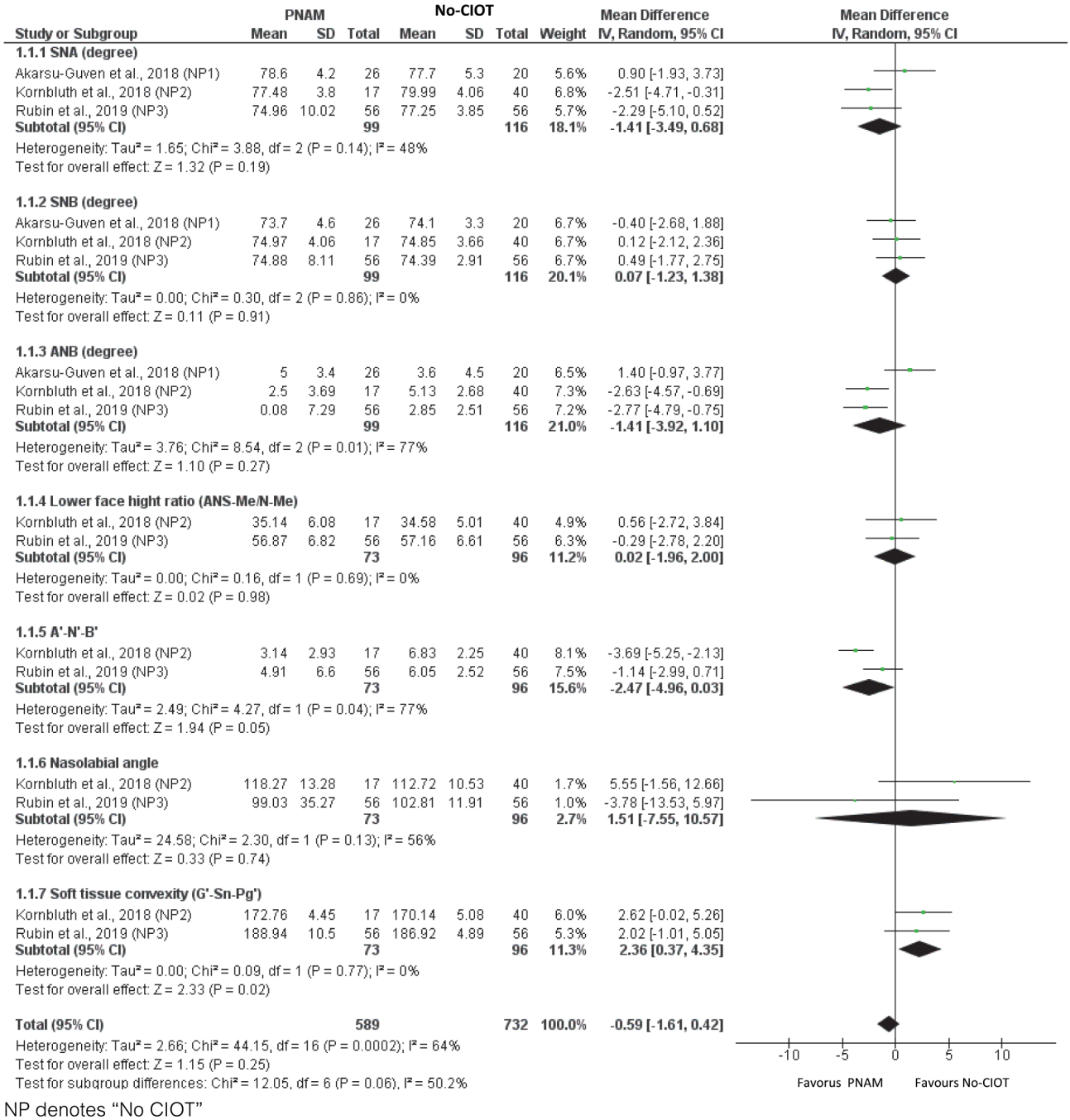
RoB was assessed with ROBINS-I [16]. All of the studies [20-23] were classified as moderate. The RoB assessment of included studies is presented in Table 3.

Cephalometric characteristics

Four studies [20-23] conforms to the inclusion criteria. All used cephalometric analysis for their evaluation (Tables 1, 2). One study [22] was excluded from the meta-analysis because of an incomplete statistical report after many failed attempts to contact the researchers. Meta-analysis demonstrated that most cephalometric parameters are not significantly different between the PNAM vs. the No-CIOT group except soft tissue convexity (Table 4). The PNAM group showed a greater soft tissue convexity angle (mean difference = 2.36; 95% CI 0.37, 4.35; Figure 2) compared to the No-CIOT group.

Table 3 Risk of bias of the included studies

Author	Pre-Intervention		At Intervention		Post-Intervention		
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results
Kornbluth *et al* [20]	Low	Low	Low	Low	Low	Moderate	Low
Akarsu-Guven *et al* [21]	Moderate	Low	Moderate	Low	Low	Low	Low
Peanchitlertkajorn *et al* [22]	Low	Moderate	Moderate	Low	Low	Low	Low
Rubin *et al* [23]	Moderate	Low	Low	Low	Low	Low	Low



NP denotes “No CIOT”

SNA represents “Anteroposterior position of maxilla in relation to anterior cranial base”

SNB represents “Anteroposterior position of mandible in relation to anterior cranial base”

ANB represents “Anteroposterior position of maxilla in relation to mandible”

A’N’B’ represents “Anteroposterior position of soft tissue of maxilla in relation to soft tissue of mandible”

Figure 2 Forest plot of cephalometric parameters between the PNAM group and the No-CIOT group

Table 4 Summary of the meta-analysis of cephalometric parameters

Cephalometric parameters	PNAM vs No-CIOT
SNA (°)	N/S
SNB (°)	N/S
ANB (°)	N/S
Lower facial height ratio (%)	N/S
A'N'B' (°)	N/S
Nasolabial angle (°)	N/S
Soft tissue convexity (°)	*

* denotes "statistically significant difference at $p<0.05$"

SNA represents "Anteroposterior position of the maxilla in relation to anterior cranial base"

SNB represents "Anteroposterior position of the mandible in relation to anterior cranial base"

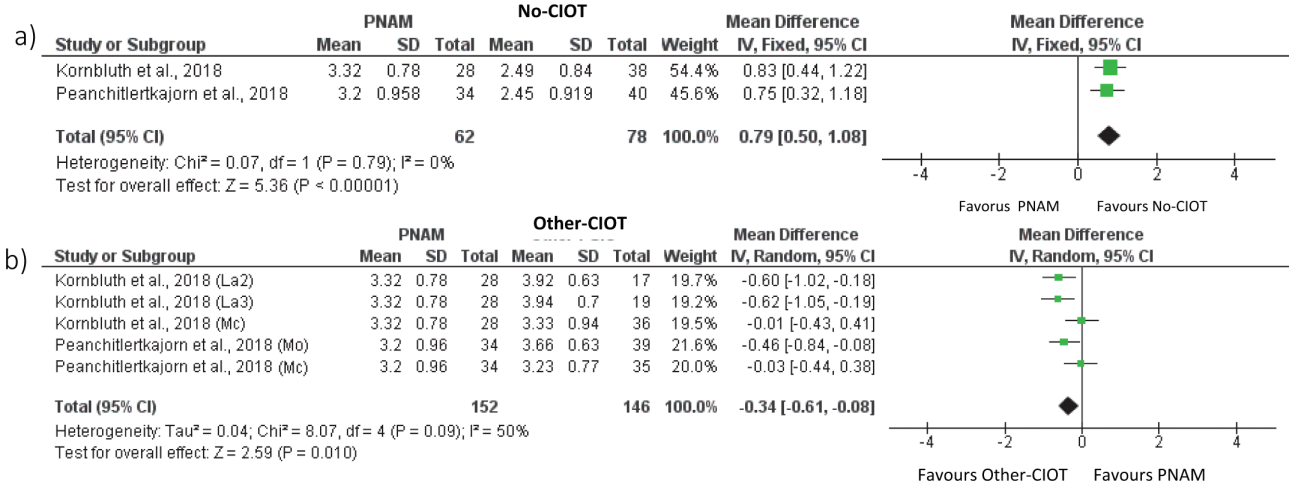
ANB represents "Anteroposterior position of maxilla in relation to mandible"

A'N'B' represents "Anteroposterior position of the soft tissue of maxilla in relation to the soft tissue of mandible"

N/S denotes "not statistically significant"

Dentoalveolar outcome

Two studies were included in this meta-analysis (Tables 1, 2) [20, 22]. The dentoalveolar outcome was measured with the GOSLON rating [24]. The GOSLON rating is the lowest in the No-CIOT group, followed by the PNAM group, and highest in the Other-CIOT group. The PNAM group shows a significantly less favorable GOSLON rating compared to the No-CIOT group (mean difference = 0.79; 95% CI 0.50, 1.08; Figure 3), but has a statistically more favorable outcome than the Other-CIOT group (mean difference = -0.34; 95% CI -0.61, -0.08; Figure 3).



La denotes "Latham appliance"

Mc denotes "Modified McNeil appliance"

Mo denotes "Molding plate

Figure 3 Forest plot of GOSLON rating between: a) the PNAM group and the No-CIOT group; b) the PNAM group and the Other-CIOT group

Publication bias assessment

All funnel plots showed a symmetrical distribution, indicating no evidence of publication bias. Linear regression-based Egger's test confirms no evidence of publication bias.

Discussion

This study focuses on the long-term treatment effects of PNAM on dentoalveolar outcomes and cephalometric characteristics. The average age of the selected studies in this systematic review ranges from 5 to 9.5 years. This study found that PNAM did not provide a significant advantage to cephalometric characteristics and dentoalveolar outcomes. Only the soft tissue convexity of PNAM has a significant advantage. These results were consistent with other systematic reviews and meta-analyses investigating the effects of CIOT [25, 26].

The GOSLON yardstick was used to assess dentoalveolar outcomes by all selected studies. The GOSLON yardstick is an easy tool for evaluating dentoalveolar relationships. The GOSLON yardstick categorized the dental study model into 5 groups based on overjet, overbite, incisal inclination, and transverse relationship (1 to 5 as excellent to a very poor outcome). It is also capable of predicting treatment needs for orthodontics alone or combined with orthognathic surgery [24, 27]. Based on our results and other similar investigations [25, 26], we believe that all CIOT including PNAM do not have significant effects on cephalometric characteristics and dentoalveolar outcome. Palatoplasty protocols [28] and primary bone grafting [27] are probably more impactful than using CIOT. This study does not examine the cost-effectiveness of PNAM. However, Alfonso *et al* reported that extra costs of PNAM could be offset by a lesser need for surgical revision [13].

The treatment results could be impacted by a variety of factors such as the PNAM initiation period. We were not able to assess the impacts of PNAM initiation age because only a few studies reported PNAM starting age (Table I) [21, 22]. The clinical adjustment of PNAM appliances is a complicated process that requires significant clinical experience. Therefore, an orthodontist's skill can affect treatment outcomes [29]. But none of the selected studies has data for further research.

Previous studies reported a significant variability of outcome evaluation methods. This prevented them from performing a meta-analysis. But our study successfully performed meta-analyses. Furthermore, this study reviewed aspects of PNAM's treatment effects that were not done. Because of a wide range of methodologies used, not all of the included research could be pooled in this meta-analysis. And samples from the included studies are mostly Whites with some Asians and Latinos. Therefore, generalization should be done carefully.

The retrospective design of the included studies is less valid to show treatment efficacy. According to the OCEBM, systematic reviews and meta-analysis of cohort studies were graded (2a) at a lower level compared to those of randomized controlled trials (1a). The lack of randomized controlled trials could be due to the difficulties of conducting this type of research. The rarity of cases and the amount of time required for follow-up make it even more difficult to do this kind of research [30]. This warrants future studies with more rigorous methods to be performed.

Conclusion

This study evaluated the treatment effects of PNAM in patients with UCLP. We found that PNAM does not enhance cephalometric characteristics and dentoalveolar outcome.

References

1. Grayson BH, Cutting CB. Presurgical nasoalveolar orthopedic molding in primary correction of the nose, lip, and alveolus of infants born with unilateral and bilateral clefts. ***Cleft Palate Craniofac J.*** 2001 May;38(3):193-198. doi:10.1597/1545-1569_2001_038_0193_pnomip_2.0.co_2.
2. Grayson BH, Cutting C, Wood R. Preoperative columella lengthening in bilateral cleft lip and palate. ***Plast Reconstr Surg.*** 1993 Dec;92(7):1422-1423.
3. Garfinkle JS, King TW, Grayson BH, Brecht LE, Cutting CB. A 12-year anthropometric evaluation of the nose in bilateral cleft lip-cleft palate patients following nasoalveolar molding and cutting bilateral cleft lip and nose reconstruction. ***Plast Reconstr Surg.*** 2011 Apr;127(4):1659-1667. doi:10.1097/PRS.0b013e31820a64d7.
4. Peanchitlertkajorn S, Mercado A, Daskalogiannakis J, Hathaway R, Russell K, Semb G, *et al*. An Intercenter Comparison of Nasolabial Appearance Including a Center Using Nasoalveolar Molding. ***Cleft Palate Craniofac J.*** 2018 May;55(5):655-663. doi:10.1177/1055665618754947.
5. Matsuo K, Hirose T, Tomono T, Iwasawa M, Katohda S, Takahashi N, *et al*. Nonsurgical correction of congenital auricular deformities in the early neonate: a preliminary report. ***Plast Reconstr Surg.*** 1984 Jan;73(1):38-51. doi:10.1097/00006534-198401000-00009.
6. Cutting C, Grayson B, Brecht L, Santiago P, Wood R, Kwon S. Presurgical columellar elongation and primary retrograde nasal reconstruction in one-stage bilateral cleft lip and nose repair. ***Plast Reconstr Surg.*** 1998 Mar;101(3):630-639. doi:10.1097/00006534-199803000-00009.
7. Sarin SP, Parkhedkar RD, Deshpande SS, Patil PG, Kothe S. Presurgical nasoalveolar moulding for a unilateral midfacial cleft: A case report. ***J Indian Prosthodont Soc.*** 2010 Mar;10(1):67-70. doi:10.1007/s13191-010-0013-1.
8. Bennun RD, Perandones C, Sepliarsky VA, Chantiri SN, Aguirre MI, Dogliotti PL. Nonsurgical correction of nasal deformity in unilateral complete cleft lip: a 6-year follow-up. ***Plast Reconstr Surg.*** 1999 Sep;104(3):616-630. doi:10.1097/00006534-199909030-00002.
9. Noor SN, Musa S. Assessment of patients' level of satisfaction with cleft treatment using the Cleft Evaluation Profile. ***Cleft Palate Craniofac J.*** 2007 May;44(3):292-303. doi:10.1597/05-151.
10. Clark SL, Teichgraeber JF, Fleshman RG, Shaw JD, Chavarria C, Kau CH, *et al*. Long-term treatment outcome of presurgical nasoalveolar molding in patients with unilateral cleft lip and palate. ***J Craniofac Surg.*** 2011 Jan;22(1):333-336. doi:10.1097/SCS.0b013e318200d874.
11. Maillard S, Retrouvey JM, Ahmed MK, Taub PJ. Correlation between Nasoalveolar Molding and Surgical, Aesthetic, Functional and Socioeconomic Outcomes Following Primary Repair Surgery: a Systematic Review. ***J Oral Maxillofac Res.*** 2017 Sep;8(3):e2. doi:10.5037/jomr.2017.8302.
12. van der Heijden P, Dijkstra PU, Stellingsma C, van der Laan BF, Korsten-Meijer AGW, Goorhuis-Brouwer SM. Limited evidence for the effect of presurgical nasoalveolar molding in unilateral cleft on nasal symmetry: a call for unified research. ***Plast Reconstr Surg.*** 2013 Jan;131(1):62e-71e. doi:10.1097/PRS.0b013e318267d4a5.
13. Alfonso AR, Ramly EP, Kantar RS, Wang MM, Eisemann BS, Staffenberg DA, *et al*. What Is the Burden of Care of Nasoalveolar Molding?

Cleft Palate Craniofac J. 2020 Sep;57(9):1078-92. doi:10.1177/1055665620929224.

14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015 Jan;4(1):1. doi:10.1186/2046-4053-4-1.
15. Group OLoEW. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine
16. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016 Oct;355:i4919. doi:10.1136/bmj.i4919
17. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods* 2006 Jun;11(2):193-206. doi: 10.1037/1082-989X.11.2.193.
18. Light RJ, Pillemer DB. Summing Up The Science of Reviewing Research: *Harvard University Press*; 1984.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997 Sep;315(7109):629-634. doi:10.1136/bmj.315.7109.629.
20. Kornbluth M, Campbell RE, Daskalogiannakis J, Ross EJ, Glick PH, Russell KA, *et al.* Active Presurgical Infant Orthopedics for Unilateral Cleft Lip and Palate: Intercenter Outcome Comparison of Latham, Modified McNeil, and Nasoalveolar Molding. *Cleft Palate Craniofac J.* 2018 May;55(5):639-648. doi:10.1177/1055665618757367.
21. Akarsu-Guven B, Arisan A, Ozgur F, Aksu M. Influence of nasoalveolar molding on skeletal development in patients with unilateral cleft lip and palate at 5 years of age. *Am J Orthod Dentofacial Orthop.* 2018 Apr;153(4):489-495. doi:10.1016/j.ajodo.2017.08.012.
22. Peanchitlertkajorn S, Mercado A, Daskalogiannakis J, Hathaway R, Russell K, Semb G, *et al.* An Intercenter Comparison of Dental Arch Relationships and Craniofacial Form Including a Center Using Nasoalveolar Molding. *Cleft Palate Craniofac J.* 2018 Jul;55(6):821-829. doi:10.1597/16-018.
23. Rubin MS, Clouston SAP, Esenlik E, Shetye PR, Flores RL, Grayson BH. Midface Growth in Patients With Unilateral Cleft Lip and Palate Treated With a Nasoalveolar Molding Protocol. *J Craniofac Surg.* 2019 Sep;30(6):1640-1643. doi:10.1097/SCS.0000000000005356.
24. Mars M, Plint DA, Houston WJ, Bergland O, Semb G. The Goslon Yardstick: a new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate J.* 1987 Oct;24(4):314-322.
25. Papadopoulos MA, Koumpridou EN, Vakalis ML, Papageorgiou SN. Effectiveness of pre-surgical infant orthopedic treatment for cleft lip and palate patients: a systematic review and meta-analysis. *Orthod Craniofac Res.* 2012 Nov;15(4):207-236. doi:10.1111/j.1601-6343.2012.01552.x.
26. Hosseini HR, Kaklamanos EG, Athanasiou AE. Treatment outcomes of pre-surgical infant orthopedics in patients with non-syndromic cleft lip and/or palate: A systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2017 Jul;12(7):e0181768. doi:10.1371/journal.pone.0181768.
27. Hathaway R, Daskalogiannakis J, Mercado A, Russell K, Long RE, Jr., Cohen M, *et al.* The Americleft study: an inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 2. Dental arch relationships. *Cleft Palate Craniofac J.* 2011 May;48(3):244-251. doi:10.1597/09-181.1.
28. Ye B, Wu Y, Zhou Y, Jing H, Hu J, Zhang G. A comparative cephalometric study for adult operated cleft palate and unoperated cleft palate patients. *J Craniomaxillofac Surg.* 2015 Sep;43(7):1218-1223. doi:10.1016/j.jcms.2015.04.015.

29. Shaw WC, Brattstrom V, Molsted K, Prahl-Andersen B, Roberts CT, Semb G. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 5: discussion and conclusions. ***Cleft Palate Craniofac J.*** 2005 Jan;42(1):93-98. doi:10.1597/02-119.5.1.

30. Long RE, Jr., Hathaway R, Daskalogiannakis J, Mercado A, Russell K, Cohen M, *et al.* The Americleft study: an inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 1. Principles and study design. ***Cleft Palate Craniofac J.*** 2011 May;48(3):239-243. doi:10.1597/09-180.1.