META-ANALYSIS OF SURGICAL TECHNIQUES FOR CLEFT PATIENTS

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Thesis
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META-ANALYSIS OF SURGICAL TECHNIQUES FOR CLEFT PATIENTS

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ABSTRACT

The objective of this study was to examine the treatment effectiveness and relapse of 3 types of maxillary surgery for cleft patients: 1. conventional orthognathic surgery (CO), 2. extraoral distraction osteogenesis (EDO), and 3. intraoral distraction osteogenesis (IDO). Twenty-four articles were used from six electronic databases: Medline, Embase, Cochrane, ISI, Scopus, and Google Scholar. Three hundred and thirty-six cephalometric measurements were examined. Finally, six measurements were investigated by meta-analysis. Heterogeneity testing, an estimation of pooled means, publication bias, and sensitivity analysis were performed.

The estimation of pooled means revealed the following results. The SNA angle at pre-treatment, post-treatment, and follow-up in the CO group was 72.6, 77.6, and 76.1 degrees, for the EDO group was 74.4, 83.3, and 83.1 degrees, for the IDO group was 73.3, 81.3, and 82.1 degrees, respectively. The SN-MP angle at pre-treatment, post-treatment, and follow-up in the CO group was 37.8, 39.9, and 38.5 degrees, for the EDO group was 35.1, 37.5, and 36.8 degrees, for the IDO group was 34.2, 38.2, and 34.6, respectively.

EDO and IDO effectiveness were similar; however, both are better than CO. After surgery, the maxilla in the CO group remained retrognathic. At 1-year follow-up, CO showed greater relapse of SNA than EDO and IDO. The mandibular plane steepness increased after surgery and rotated counter-clockwise at 1-year follow-up in all groups.

KEY WORDS: ORTHOGNATHIC SURGERY / EXTRA-ORAL DISTRACTION / INTRA-ORAL DISTRACTION / CLEFT LIP CLEFT PALATE / META-ANALYSIS

77 pages

การวิเคราะห์เมตาเปรียบเทียบวิธีการผ่าตัดชนิดต่างๆในผู้ป่วยปากแหว่งเพดานโหว่
META-ANALYSIS OF SURGICAL TECHNIQUES FOR CLEFT PATIENTS

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บทคัดย่อ

วัตถุประสงค์ของการศึกษานี้เพื่อศึกษาประสิทธิผลการบำบัดรักษาและการถอยกลับของวิธีการผ่าตัดขากรรไกรบนสำหรับผู้ป่วยปากแหว่งเพดานโหว่ทั้งสามชนิด: 1. การผ่าตัดแบบอนุรักษ์ (CO), 2. การผ่าตัดโดยใช้เครื่องมือยึดกระดูกภายนอกช่องปาก (EDO), และ 3. การผ่าตัดโดยใช้เครื่องมือยึดกระดูกภายในช่องปาก (IDO) ภายหลังจากสืบค้นบทความในฐานข้อมูลทางอิเล็กทรอนิกส์จำนวนหกฐานข้อมูลซึ่งประกอบไปด้วย Medline, Embase, Cochrane, ISI, Scopus, และ Google Scholar ข้อมูลจากยี่สิบสี่บทความได้ถูกนำมาตรวจสอบถึงตำแหน่งอ้างอิงจากภาพถ่ายกระโหลกศรีษะด้านข้างจำนวนสามร้อยสามสิบหกตำแหน่ง ท้ายสุดแล้วมีเพียงหกตำแหน่งอ้างอิงที่สามารถนำมาวิเคราะห์ทางเมตาต่อไปได้ การวิเคราะห์ประกอบไปด้วย heterogeneity test, estimation of pooled means, publication bias, และ sensitivity analysis

การประมาณค่ากลางได้ผลการวิเคราะห์ดังนี้ มุม SNA ก่อนการรักษา, ภายหลังการรักษา, และการติดตามผลการรักษาในกลุ่ม CO ได้ค่าเป็น 72.6, 77.6, และ 76.1 องศา ในกลุ่ม EDO ได้ค่าเป็น 74.4, 83.3, และ 83.1 องศา ในกลุ่ม IDO ได้ค่าเป็น 73.3, 81.3, และ 82.1 องศา มุม SN-MP ก่อนการรักษา, ภายหลังการรักษา, และการติดตามผลการรักษาในกลุ่ม CO ได้ค่าเป็น 37.8, 39.9, และ 38.5 องศา ในกลุ่ม EDO ได้ค่าเป็น 35.1, 37.5, และ 36.8 องศา ในกลุ่ม IDO ได้ค่าเป็น 34.2, 38.2, และ 34.6 องศา

ประสิทธิผลของวิธีผ่าตัดแบบ EDO และ IDO มีความคล้ายคลึงกันแต่ดีกว่าวิธีผ่าตัดแบบ CO กระดูกขากรรไกรบนภายหลังการรักษายังคงอยู่ในตำแหน่งถอยหลัง ภายหลังการติดตามผล 1 ปี พบมีการถอยกลับของค่ามุม SNA ในกลุ่ม CO มากกว่ากลุ่ม EDO และ IDO ทั้งนี้ยังพบมีการหมุนของขากรรไกรล่างตามเข็มนาฬิกาภายหลังการผ่าตัด และหมุนทวนเข็มนาฬิกาภายหลังการติดตามผลการรักษาเป็นระยะเวลา 1 ปี ในทุกกลุ่มของการผ่าตัด

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CHAPTER I
INTRODUCTION

1.1 Background

Many complete cleft lip and palate (CLP) patients usually present with maxillary hypoplasia in all dimensions, class III skeletal relationship, facial asymmetry, class III dental malocclusion, concave or "dish face" facial profile, and soft tissues deformities of lip and nose.(Figure 1.1) Functional deficits sometimes involve speech, hearing, periodontal, and dental destruction, etc.(Ross 1987; Bevilacqua, Ritoli et al. 2008) The causes of maxillary hypoplasia could be due to reduced growth of both soft tissue and hard tissue from congenital cleft defect, and the sequels of scar contraction from the primary lip and palate repair during infancy.(Ross 1987)

Figure 1.1 Characteristics of patient with severe midface deficiency

Many of these cases required combined orthodontics and orthognathic surgery to correct the dentofacial deformities. The treatment need for maxillary advancement in adult cleft patients was reported to be around 25-60%.(Panula, Lovius et al. 1993; Turvey, Vig et al. 1996)

Conventional orthognathic surgery using LeFort maxillary surgery (with or without bone graft or in combination with mandibular surgery) has been used for moderate to severe midface deficiency in cleft patient. The maxilla is usually moved in the forward and downward position, however, the amount of movement was quite limited.(Bralley and Schoeny 1977) In spite of efforts to improve stability by using block bone graft in the posterior gap between the maxillary tuberosity and the pterygoid plates or using rigid surgical fixation, there was great tendency to relapse in cleft patients compared to non-cleft patients.(Obwegeser 1969; Houston, James et al. 1989; Turvey, Vig et al. 1996; Heliovaara, Ranta et al. 2002)

Distraction Osteogenesis (DO) has become a new treatment modality for advancement of the maxilla in CLP patients. In this technique, the maxilla would be gradually advanced by distractor into the desired direction. Many literatures reported that DO enhanced the amount of maxilla advancement.(Cohen, Burstein et al. 1997) Therefore, concurrent mandibular osteotomy was less frequently required. The stability of distracted bone was better than conventional orthognathic surgery and there was no need for intermediate bone graft. DO tends to be preferred for younger CLP patients with more severe deformities.(Figueroa, Polley et al. 2004; Cheung and Chua 2006; Cheung, Chua et al. 2006; Kanno, Mitsugi et al. 2008; Chua, Hagg et al. 2010) Other advantages of maxillary distraction is the positive soft tissue changes by increasing the nasal projection, normalizing the nasolabial angle, and making the upper lip more prominent.(Wen-Ching Ko, Figueroa et al. 2000; Harada, Baba et al. 2002)

Nowadays, midface distraction tools can be divided into 2 major groups; (1) the external type distractor,(Figueroa, Polley et al. 2004; Molina 2004; Yamauchi, Mitsugi et al. 2006) and (2) the Internal type distractor.(Chin and Toth 1997; Cohen, Burstein et al. 1997; Rachmiel, Aizenbud et al. 2005; Cheung, Chua et al. 2006) Due to expensive cost of distraction device, many surgeon and orthodontist may be reluctant to choose DO surgical treatment for every cleft patient. They may also feel uncertain about many factors that might influence the treatment results.

At present there were only a few numbers of clinical researches made to compare conventional orthognathic surgery and distraction osteogenesis.(Baek, Lee et al. 2007; Chanchareonsook, Whitehill et al. 2007; Kanno, Mitsugi et al. 2008; Chua, Hagg et al. 2010) Among these, only 2 papers were designed as randomized controlled trial.(Cheung, Chua et al. 2006; Chua, Hagg et al. 2010) Nonetheless, there was no paper reported the comparison of effectiveness among conventional orthognathic surgery, extra-oral distraction osteogenesis, and intra-oral distraction osteogenesis.

Meta-analysis is a systematic method that uses statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. (Alderson and Green) (Alderson and Green) (Alderson and Green) So far, only 1 paper claimed to have done meta-analysis concerning surgical technique in cleft patient.(Cheung and Chua 2006) However, the paper did not show actual statistic meta-analysis. Pooling outcomes could be more useful information in clinical practice.

Our research questions were related to the treatment effectiveness and stability results of 3 contemporary surgical techniques to advance the maxilla of cleft patients.

1.2 Definition used by this study

Meta-analysis refers to the analysis of quantitative studies by statistical procedure introduced by (Glass GV, McGaw B, Smith ML)(Glass, McGaw et al. 1981).

Osteotomy refers to the sawing or cutting of a bone. Kinds of osteotomy include block osteotomy, in which a section of bone is excised; cuneiform osteotomy to remove a bone wedge; and displacement osteotomy, in which a bone is redesigned surgically to alter the alignment or weight-bearing stress areas. (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier)

Distraction osteogenesis (also called callus distraction, callotasis, or osteodistraction)refers to a surgical process used to reconstruct skeletal deformities and lengthen the long bones of the body. A corticotomy is used to fracture the bone into two segments, and the two bone ends of the bone are gradually moved apart during the distraction phase, allowing new bone to form in the gap. When the desired or possible length is reached, a consolidation phase follows in which the bone is allowed to keep healing. Distraction osteogenesis has the benefit of simultaneously increasing bone length and the volume of surrounding soft tissues(Tavakoli, Stewart et al. 1998).

Cephalometry refers to scientific measurement of the head, such as that performed in dentistry to determine appropriate orthodontic procedures for correcting malocclusions and other abnormal conditions. (Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier)

1.3 Significance of the study

1. Improvement of surgeon and orthodontist decision about choosing appropriate surgical treatment for cleft patient with severe maxillary hypoplasia.
2. Provide the direction for future research for cleft patients.
3. This study can be an exemplar for future synthesis of other research by using meta-analysis.

CHAPTER II
OBJECTIVES

The objective of this study was to examine the cephalometric characteristics of cleft patient at pre-treatment, post-treatment, 1 year follow-up, the treatment change, the relapse change, and the relapse rate, among 3 types of maxillary surgery; which were (1) conventional LeFort orthognathic surgery (CO), (2) extraoral distraction osteogenesis (EDO), and (3) intraoral distraction osteogenesis (IDO), in cleft patients, using descriptive meta-analysis.

CHAPTER III
LITERATURE REVIEW

This study is emphasize pre-treatment characteristics, treatment change and stability of cleft patient who underwent Le Fort I or II conventional osteotomy and Le Fort I or II distraction osteogenesis using meta-analysis technique. This review literature in this chapter covers issues related to the cleft palate surgery and meta-analysis technique.

3.1 Incidence of cleft lip and cleft palate

Cleft lip and palate is a congenital deformities and this can be a significant health problem in the world. (Figure 3.1) Cleft lip and palate are present in one of 1,000 live Caucasian births. The incidence of cleft palate alone is one in 500 live births.(Murray 2002) Considering the cleft deformities of all races grouped together, 50% are cleft lip and palate, 30-35% are palate only, and 15-20% are cleft lip only. The genetics of cleft lip and palate are not classical Mendelian, but siblings of cleft patients are at greater risk. The risk is directly related to the frequency and severity of the clefts. Approximately 10% of patients with a cleft deformity will have other anomalies at birth(Vanderas 1987).

Figure 3.1 Patients with unilateral (left) and bilateral (right) cleft lip and palate (CLP)

Patients with cleft lip and palate (CLP) usually present with collapsed maxillary dental arch and impaired forward growth of the maxilla as a result of scar tissue from the early surgical repair of CLP(Ross 1987). Many of these patients exhibit varying degree of three-dimensional deficiency of maxilla and compensatory growth of mandible. The conditions, if severe, require jaw surgery to improve facial esthetics, normalize speech articulation, and improve quality of life. In many cases, these problems required orthodontic treatment combined with orthognathic surgical procedures such as Le Fort I osteotomy or distraction osteogenesis.(Adlam, Yau et al. 1989)

Ross showed that about 25% of patients with unilateral cleft lip and palate develop maxillary hypoplasia that does not respond to orthodontic treatment alone. It is known that 25% to 60% of all patients born with cleft lip and palate will require maxillary advancement to correct the maxillary hypoplasia and improve esthetic facial proportions.(Panula, Lovius et al. 1993; Turvey, Vig et al. 1996)

3.2 Characteristics of cleft lip and palate(Turvey TA, Vig KWL et al. 1996)

Dento-facial characteristics of cleft lip and palate patients are as follows.

3.2.1 Skeletal

3.2.1.1 Maxilla

Maxillary hypoplasia

Alveolus Maxillary hypoplasia

Premaxilla malposition

Alveolar Cleft

3.2.1.2 Mandible

Over-closure or backward rotation of mandible

Mandibular growth disturbance

Max-Mand relationship

Skeletal class III

3.2.1.3Others

Asymmetry (Unilateral)

Maxillary canting and asymmetry
Compensatory mandibular asymmetry

3.2.2 Dentition

Anterior class III malocclusion
Anterior and/or posterior cross bite
Teeth malalignment
Missing teeth
Malformed teeth
Dental crowding
Complex malocclusion

3.2.3 Soft tissue

Concave profile

Midface deficiency is common in cleft palate patient. Cleft palate surgery leaves area of denuded palatal bone to granulate, and the consequent scarring may result in underdevelopment and deformation of the maxilla.

3.3 Surgical procedure of cleft palate

In general Facial skeletal disproportion may be addressed two ways. Both techniques are useful but have separate indications. They are commonly used together for patients with cleft malformations (Turvey TA, Ruiz RL et al. 2002).

3.3.1 Conventional LeFort Orthognathicsurgery (maxillary advancement and inferior repositioning: CO) (Figure 3.2)

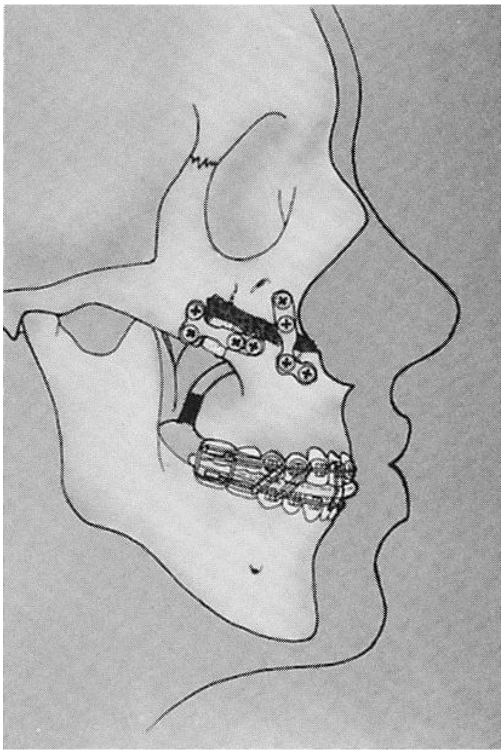

Figure 3.2 Conventional LeFort orthognathic surgery (CO)(Bell 1992)

The most common dentofacial deformity associated with cleft lip and palate is maxillary deficiency. Thus, the usual surgical approach is LeFort I Maxillary advancement and inferior repositioning. The patients who has previously undergone alveolar reconstruction can performed LeFort I without any other alveolar anterior maxillary reconstruction.

These have been numerous studies about long term stability and/or relapse of maxillary advancement surgery with LeFort I osteotomy (MAL)(Araujo, Schendel et al. 1978; Drommer and Luhr 1981; Garrison, Lapp et al. 1987; Posnick and Ewing 1990; Louis, Waite et al. 1993; Cheung, Samman et al. 1994; Posnick and Dagys 1994; Posnick and Taylor 1994; Proffit, Turvey et al. 1996; Van Sickels and Richardson 1996; Gurstein, Sather et al. 1998; Heliovaara, Ranta et al. 2002; Dowling, Espeland et al. 2005). The amount of relapse for MAL in non-cleft patients with maxillary hypoplasia is known to be 10%(Hoffman and Brennan 2004). However, compare with non-cleft patients, patients with CLP shown much higher rates of relapse from 25% to 50%(Kufner 1971; Epker and Wolford 1976; Champy 1980;

Drommer and Luhr 1981; Eskenazi and Schendel 1992; Hirano and Suzuki 2001; Baumann and Sinko 2003; Cheung and Chua 2006).

Problem associated with long term stability of MAL in patients with CLP have been attributed to retraction of scar tissue, tightness of the upper lip, interference with the nasal septum, inadequate mobilization of the bony segment, and thin and fragile bony structures of the lateral piriform wall and zygoma base for rigid fixation(Welch 1989; Posnick and Dagys 1994).

3.3.2 Distraction Osteogenesis (DO)

Distraction osteogenesis (DO), a useful technique to generate bone and soft tissue, can be applied to craniofacial reconstruction, including orthognathic surgery, cleft lip and palate reconstruction, a new mandibular condyle regeneration, a dentoalveolar unit reconstruction for dental implants, and transport DO for discontinuity defects. The distraction technique involves creating an osteotomy in an area adjacent to an area of bone deficiency. Applying slow tension forces separates the bony edges, which creates a regenerate chamber from which the new bone and soft tissues are formed.

According to Ilizarov principles (Ilizarov 1988), the principles of Distraction osteogenesis (DO) includes:

1. Osteotomy of the bone site with minimal periosteal stripping
2. Latency period: 3, 5, or 7 days, depending on the surgical site
3. Distraction rate: 1.0 mm per day (0.5–2.0 mm)
4. Distraction rhythm: continuous force application is best, yet device activation twice a day is more practical and allows for better patient compliance
5. Consolidation: until a cortical outline can be seen radiographically across the distraction gap, usually 6 weeks

The application of distraction osteogenesis in the maxillofacial region is gaining popularity. Maxillary distraction osteogenesis (MDO) has become an alternative option for treatment of maxillary hypoplasia in patients with CLP(Cohen, Corrigan et al. 1995) and can be used in growing patients.(Rachmiel, Aizenbud et al. 2005; Wang, Wang et al. 2005)

Distraction osteogenesis devices for CLP can be classified as follows.

3.3.1.1 External distractor: EDO (Figure 3.3)

3.3.1.2 Internal distractor: IDO (Figure 3.4)

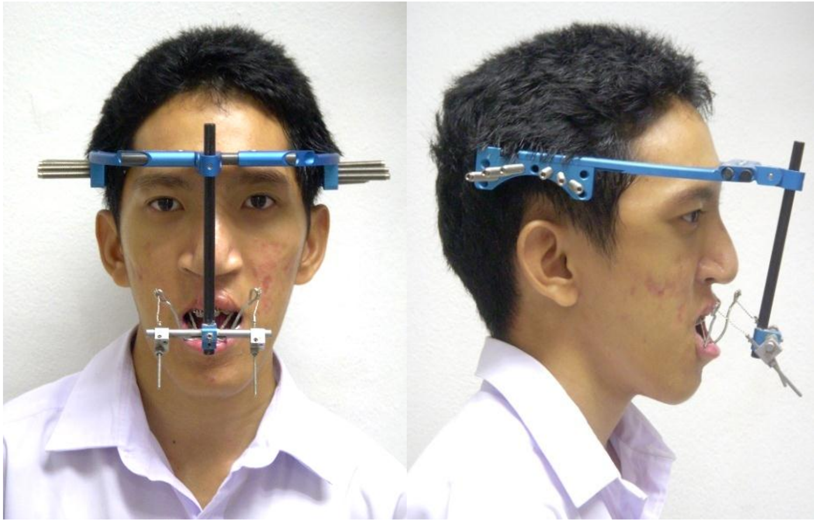

Figure 3.3 Distraction Osteogenesis (external distractor: EDO)

Figure 3.4 Distraction Osteogenesis (internal distractor: IDO)**(Synthes 2002)**

However, it remains controversial whether distraction osteogenesis using devices has better results and stability than conventional orthognathic surgery, particularly in patients with CLP.

3.4 Meta-analysis

3.4.1 Definition

Meta-analysis refers to the analysis of analysis(Glass 1976). Glass, et al.(Glass, McGaw et al. 1981) described meta-analysis as the attitude of data analysis applied to quantitative summaries of individual experiments. Meta-analysis also refers to a review of literature that has as its aim the quantitative integration of results from multiple primary studies relevant to a single research question. In summary, meta-analysis is a quantitative approach for systematically combining the results of previous research in order to arrive at conclusions about the body of research.

3.4.2 Overall Goals, Main uses and Description of Steps

The overall goal of meta-analysis is to integrate the results of previous studies to arrive at summary conclusions about a body of research. It is most useful in summarizing prior research when individual studies are small and they are individually too small to yield a valid conclusion.

Meta-analysis serves to integrate empirical research, synthesize research findings, and organized research results into coherent patterns.(Glass, McGaw et al. 1981) It makes explicit the state of knowledge on a question in term of what a body of research literature does and does not reveal.(Smith and Naftel 1984)

Meta-analysis is addressed to solve the problems of traditional literature reviews, which are(Wolf 1986):

3.4.2.1 Selective inclusion of studies, often based on the reviewer’s own impressionistic view of the quality of the study

3.4.2.2 Differential subjective weighting of studies in the interpretation of a set of findings

3.4.2.3 Misleading interpretations of study findings

3.4.2.4 Failure to examine characteristics of the studies as potential explanations for disparate or consistent results across studies

3.4.2.5 Failure to examine moderating variables in the relationship under examination

Meta-analysis has been applied most often to combine the results of randomized trials. However, there are many topics for which randomized trials are impossible. For example, smoking and alcohol use cannot be assigned at random. Meta-analysis of nonexperimental studies is also common. For nonexperimantal studies, the method is also most useful when there are many studies with low statistical power.

There are five main steps in meta-analysis. First, formulating the research problem or hypothesis. Second, selecting the data base of studies. Third, describing, classifying and coding the studies. Fourth, measuring study finding by transform the finding into a common effect size. Fifth, the abstracted data are analyzed statistically.

3.4.3 Methodology of meta-analysis

The methodology for meta-analysis has similar and paralleled to the primary research(Smith and Naftel 1984):

3.4.3.1 Formulating the research problem or hypothesis

Sources for the meta-analysis question can include a) theory bearing on the topic, b) prior research, c) the primary research expected to be reviewed, and d) the intellectual resources of the reviewer.(Jackson 1980) This phase also encompasses formulation of a tentative question or hypothesis, identification of elements referent to the inquiry, identification of related fields of knowledge, specification of archival sources and scholars in the field, specification of a working bibliography, and a broad conceptualization for term of the meta-analysis.

3.4.3.2 Selecting the data base of studies

In meta-analysis, the study serves as the unit of research endeavor; the findings transformed into common metric (effect size) are the dependent variables; and the methodological and substantive characteristics of the study are the independent variables. This phase involved a decision regarding the sample or population, specification of the study sources, refinement of the terms, specification of the methodological and substantive characteristics to be examined, development of criteria for study quality, refinement of the problem question and propositional hypotheses, and construction of the preliminary codebook. No matter how sophisticated the statistical techniques used to aggregate data from studies, a review does not qualify as meta-analysis unless the procedures to identify studies are both systematic and explicit.

3.4.3.3 Describing, classifying and coding the studies

The elements of the studies to be elevated and coded are the findings (data for calculating effect sizes) and the methodological and substantive characteristics. This phase requires the most labor and major difficulty is not finding sufficient data for extraction of elements. A careful reading of all the articles is mandatory. Adequate attention should be paid to identify articles base on the same group of patients, or using sub-group of subjects already considered in other studies. The inclusion in the analysis of groups of subjects who are not independent will lead to a selection bias.

3.4.3.4 Measuring study finding by transform the finding into a common metric effect size.

The results of a trial may be expressed as odds ratio (OR) or risk difference (RD), which is also known in epidemiology as absolute risk reduction (ARR). As meta-analysis is a way of aggregating the results of multiple trials, the result obtained may be expressed as pooled odds ratio (ORp) or pooled risk difference (RDp).

In order to pool the results of the different studied, we should assume that these results would give an evaluation of effect, which would be the same for all studies, and that the effects evaluated would be part of the same distribution. This assumption should be verified with a statistical test, the test for heterogeneity. If this is correct, in a future analysis we can use formulas based on this assumption, called fixed effect models. If we are not constrained by the studied belonging to the same population, and therefore we assume that the variability of the results depends on the variability of the intra- and inter-studies, we will use procedures called random effects models.

Other statistical procedures are the test for publication bias, sensitivity analysis, the number needed to treat (NNT), and the cumulative meta-analysis.

3.4.3.5 Interpreting and reporting the results

The interpretation of results obtained with a meta-analysis is the results of a series of evaluations that start from the evaluation of the size of pooled effect, the possible cause of heterogeneity, the evaluation of the stability of the mata-analysis, and the calculation of the number need to be treated.

This phase is analogous to primary research. The result of this phase is either a qualified response to the problem question or an explanation as to why the question cannot be answered and what needs to be done to answer it. The results can generate further primary research or for future reviews.

3.4.4 Limitation of Meta-analysis

In addition to these advantages, however, meta-analysis has some limitations(Glass, McGaw et al. 1981):

3.4.4.1 Logical conclusion cannot be drawn by comparing and aggregating studies that include different measuring techniques, definitions of variables, and subjects, because the studies are often too dissimilar. This is also called “apple and oranges” problem.

3.4.4.2 Results of meta-analysis may be uninterpretable because results from poorly designed studies are included along with results from well design studies.

3.4.4.3 Research published in journals is biased in favor of statistically significant findings because nonsignificant findings are rarely published; therefore, this can lead to bias meta-analysis results as well.

3.4.4.4 Multiple results or outcomes from the same study are often used, which may bias or invalidate the meta-analysis and make the results appear more reliable than they really are, because these results are not independent.

Mainly coding procedures or specific characteristics, and then applying statistical tests for difference can deal with the first and second criticism. Coding the quality of a research design and weighting for design quality and sample size can also be similarly employed for accessing the worthiness of results.

The third criticism can be dealt with by expanding literature reviews to include research findings in books, dissertations, unpublished papers presented at professional meetings, etc., and by comparing these finding to those of published journal articles.

Several different approaches may be used to deal with the fourth criticism and for each different outcome tested. It is also possible to limit to a fixed number the results that may be utilized from studies.

3.5 Meta-analysis in cleft patients

Cheung, et al. (Cheung and Chua 2006) had done descriptive meta-analysis on cleft surgical techniques. They conclude that there is still no conclusive data on any differences in surgical relapse, velopharyngeal function and speech between conventional osteotomy and distraction osteogenesis. Both techniques can deliver a marked improvement in facial aesthetics. So far, only 1 meta-analysis research is available (Cheung and Chua 2006) but this meta-analysis did not pool the outcome for each surgical technique.

CHAPTER IV
MATERIALS AND METHODS

This meta-analysis was based on the PRISMA Statement for reporting systematic reviews and meta-analyses of studies.(Liberati, Altman et al. 2009) So far, there was no previous protocol and registration related to the maxillary surgery for cleft patients.

4.1 Search strategy

Six electronic databases (Embase, Medline, ISI, Cochrane, Scopus, and Google Scholar) were searched for all years until April 2010. Restrictions were made for English publications. Search strategies are constructed based on type of patients, use of surgical technique, and outcome measures (PICOS) using following key words; [cleft] and [maxilla or maxillary] and [osteotomy or distraction or advancement or orthognathic surgery] and [measurement or cephalometry or cephalometric or analysis or cephalograph or cephalographs](Appendix A). Dissertations and conference proceedings retrieved from electronic database were included. In addition, secondary references from reference lists of review articles and meta-analyses were manually examined and any papers of interest by title or author were retrieved for possible inclusion.

All citations from six databases were exported to EndNote® program (Version X4, California, USA). Duplications were removed using EndNote® (Command: find duplicates) followed by manually double check by T.P.

Two reviewers (N.V. and T.P.) independently screened abstracts using inclusion, exclusion, and ineligibility criteria as demonstrated in Table 4.1. Any disagreement was resolved by consultation until a final consensus was achieved. After abstract screening, selected abstract would be search for full text papers for further cephalometric values related to surgical maxillary advancement.

Table 4.1 Inclusion, exclusion, and ineligibility criteria

Inclusion criteria	Exclusion criteria	Eligibility criteria
1. Randomized controlled clinical trials (RCTs)	**1.** Non-English publication	**1.** Characteristics of patient not associated
2. Observational studies (e.g. cohort studies, cross sectional studies, case series, case report ≥ 2 cases)	**2.** Animal research	**2.** Treatment strategies not associated
	3. Commentary / Review article / Systematic review/ 1 case report	**3.** Treatment outcome not associated
	4. Insufficient data (e.g. repeated abstract from same paper, thesis that found published paper, repeated samples by multiple publication, and statistical technique problems)	**4.** Research Methodology not associated

4.2 Cephalometric measurements

Because suggestion and the cephalometric values reported in literatures were varied tremendously, preliminary screening was necessary to check adequacy of the numbers of papers. Overall 336 dento-skeletal cephalometric values were screened, comprising pre-treatment, post-treatment, follow-up (1 year), treatment changes, relapse changes and relapse rate (Appendix B part C). The alphabets C, E, and I represent conventional orthognathic surgery, extraoral distraction, and intraoral distraction respectively.

4.3 Data extraction

Data extraction was independently performed by two reviewers (N.V. and T.P) according to a standardized data extraction forms.(Appependix B) Any disagreement between the two would be solved by discussion. Those paper reporting sample size, values of mean, standard deviation, or a raw data would be eligible for data collection.

Risk of bias in individual studies was assessed both at the methodology and outcome level of studies. Precautions had been exercised to ensure homogeneity of data as much as possible in our study. For example, repeated publication or any papers with possibility of using the same pool patients would be discarded. In the absence of reported summary statistics such as in case series or case reports, the required variables would be calculated by the author. If there was any doubt, such as the mean values of mixed cleft and non-cleft patients or mixed intraoral and extraoral distractor, the examiners would look back into the raw data of each patient and selected the variables which matched the inclusion criteria. In these scenarios, recalculation for the new means and standard deviations were made using SPSS® program (version 18, New York, USA). In addition, the error of measurements of each study would be examined.

4.4 Statistical analysis

The software "Comprehensive Meta-Analysis V2" (Biostat Inc., Englewood, New Jersey, USA) was used. Means of cephalometric measurements were pooled according to CO, EDO, and IDO techniques. The steps of analysis were as follows.

4.4.1 Heterogeneity test (Forest plots, Q value, and I^2 index)

Mean of cephalometric measure was pooled. Forest plot was graphed to visually assess heterogeneity across studies. Heterogeneity of means was assessed using Q test and a degree of heterogeneity was quantified using I^2 statistic.

The heterogeneity was defined as low (25%), moderate (50%), or high (75%).(Higgins, Thompson et al. 2003) Heterogeneity was present if P value < 0.10 or the $I^2 \geq 25\%$ would be considered significant.(Huedo-Medina, Sanchez-Meca et al. 2006) Pooling mean was estimated using a fixed effect model if there was no evidence of heterogeneity otherwise the random effect model was applied. Each study was weighted by inverse variance of mean, which estimated using within-study variance for the fixed effect model and within-study plus between-study variances for the random effect model.

4.4.2 Publication bias (Funnel plot and Egger's test)

Publication bias was examined either by funnel plots or linear-regression-based Egger's test.

4.4.2.1 Funnel plot

Publication bias was either evaluated through visual inspection of funnel plots asymmetry or outlier data.(Light and Pillemer 1984) The mean results from each study were plotted against standard error. If there was no bias then small studies should be spread out symmetrically around the pooled mean estimate. If there was publication bias then the small studies would be clustered over to one side and the plot would be considered as asymmetric.

4.4.2.1 Egger's test

The Egger's test was also used to statistically assess whether the funnel plot was asymmetry. If it was significant (P value < 0.05), there might be publication bias due to missing some studies. Meta-trim and filled was therefore applied to impute missing studies.

4.4.3 Sensitivity analysis

Sensitivity analysis was performed by excluding study might be a source of publication bias or heterogeneity (suggested from funnel plots or meta-regression) or poor quality studies from the main analysis. Results were then compared.

4.4.4 Indirect comparison of pooled mean

Pooled mean along with its 95% CI of each cephalometric value was plotted by CO, EDO, and IDO techniques. Indirect comparison was then visually inspected. The pooled means were statistically significant if their CIs were not overlapped or the mean difference was clinically greater than 1.5 degrees.

4.4.5 Subgroup analysis

Subgroup analyses would be performed by the approach of Deeks et al.(Deeks, Altman et al. 2008) The following subgroups were defined prior to data analyses which were age, cleft type, pharyngeal flap, and secondary alveolar bone graft.

4.4.6 Calculation for treatment change, relapse change, and relapse rate

The results of the pooled mean estimate from meta-analysis would be used for calculation of treatment change, relapse change, and relapse rate. Treatment change was calculated from the pooled mean estimate difference between pre-treatment and post-treatment. Relapse change was calculated from the pooled mean estimate difference between post-treatment and follow-up. The amount of relapse rate (percentage) would be calculated using the following formula.

$$\textbf{Relapse rate} = \frac{\textbf{Relapse change}}{\textbf{Treatment change}} \times \textbf{100\%}$$

CHAPTER V

RESULTS

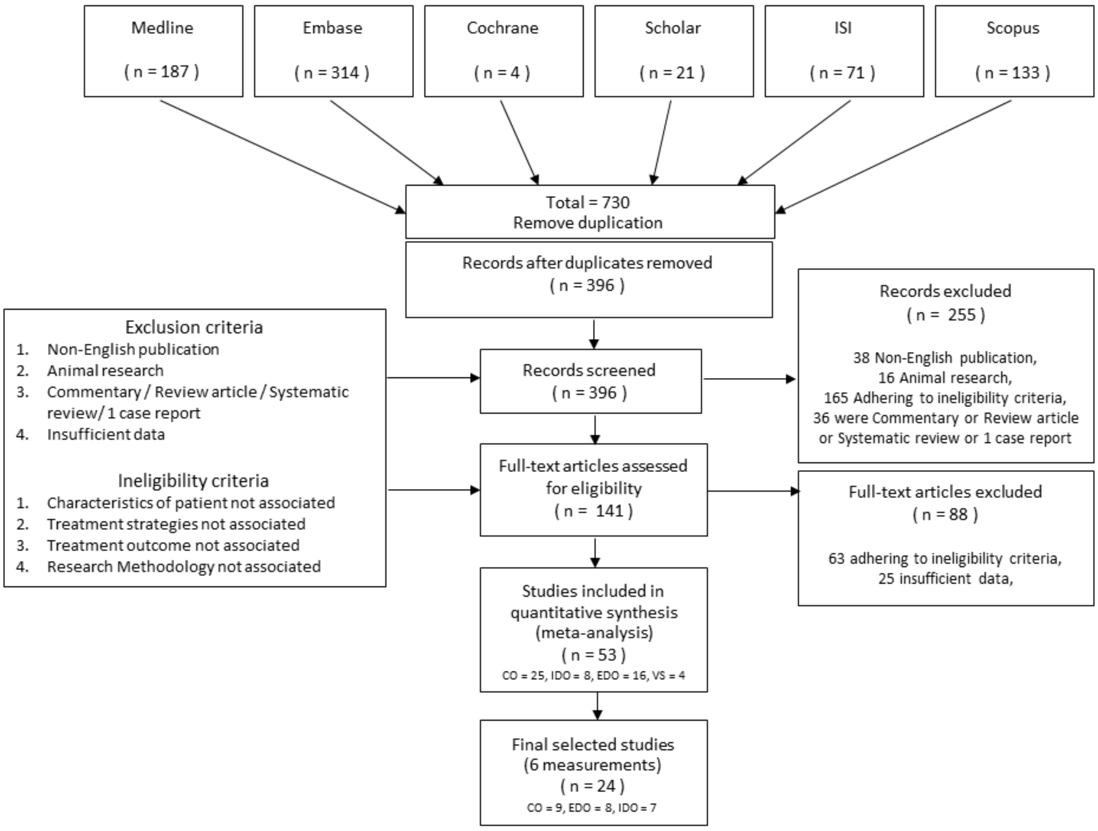

Figure 5.1 PRISMA flow diagram

The numbers of studies screened at each stage are presented in the flow diagram of search strategies process. (Figure 5.1) Overall, 730 citations were exported to EndNote® program (Version X4, California, USA). Duplications were removed using EndNote® (Command: find duplicates) followed by manually double check by T.P., which reduced the numbers of eligible abstract down to 396 abstracts.

Two reviewers (N.V. and T.P.) independently screened 396 abstracts using inclusion, exclusion, and ineligibility criteria as demonstrated in Table 4.1. Any disagreement was resolved by consultation until a final consensus was achieved. Inter-reviewer agreement on study eligibility was 96.2% (381/396). After abstract screening, only 141 full text papers were retrieved and examined in search of studies. At this stage, there was only 3.5% (5/141) disagreement between two reviewers.

Finally, 53 papers were selected for further data extraction, which could be classified as followed; 1) conventional orthognathic surgery alone (CO: n=25), 2) extraoral distraction osteogenesis alone (EDO: n= 16), 3) intraoral distraction osteogenesis alone (IDO: n=8), and 4) comparative studies with at least 2 surgical techniques (n=4). Those paper reporting sample size, values of mean, standard deviation, or a raw data would be eligible for data collection. Overall 336 dento-skeletal cephalometric values were screened. The distributions of numbers of papers found for each cephalometric value were listed after each surgical treatment technique.(Table 5.1)

Using the criteria that the cephalometric values must be available across 3 surgical treatment techniques, and at least 3 papers must be present for each group, only 6 values which were SNA and SN-MP as demonstrated in Figure 5.2, at pre-treatment, post-treatment, and follow-up were considered eligible for further meta-analysis.

Table 5.1 The distributions of articles found for cephalometric measurements, classified by 3 surgical techniques

	Cephalometric Value	Pre-treatment	Post-treatment	Follow-up	Treatment changes	Relapse changes	Relapse rate
Angle Skeletal Measures	SNA	C11, I8 , E8	C11, I8 , E8	C7, I4 , E6	C4 , I7 , E2	C2 , I3	-
	SNB	C7 , I2 , E5	C7 , I2 , E5	C4 , I2 , E6	C2 , I2 , E1	I2 , E1	-
	ANB	C6 , I2 , E5	C6 , I2 , E5	C3 , I2 , E5	C2 , I2 , E1	I2 , E1	-
	FH-PP	C2 , E1	C2 , E1	C2 , E1	C1 , E1	C1 , E1	-
	FH-FO	-	-	-	-	-	-
	FH-MP	-	-	-	-	-	-
	SN-PP	C6 , E1	C6 , E1	C4 , E1	C1	C1	-
	SN-FO	-	-	-	-	-	-
	SN-MP	C5 , I3 , E6	C5 , I3 , E6	C4 , I3 , E5	I2 , E1	I2	-
	MP-PP	C2 , E1	C2 , E1	C1 , E1	-	-	-
	NAPg	I1 , E1	I1 , E1	E1	I1 , E1	E1	-
	SNPg	C3	C3	C3	-	-	-
	LFH ratio	I1 , E1	I1 , E1	I1 , E1	-	-	-
Linear Horizontal Skeletal Measures	AO-BO	-	-	-	-	-	-
	A to Nper	C1 , I3 , E2	C1 , I3 , E2	C1 , I2 , E2	C3 , I2 , E1	C3 , I1 , E1	-
	B to Nper	-	-	-	-	-	-
	ANS to Nper	E1	E1	E1	-	-	-
	PNS to Nper	-	-	-	-	-	-
	A to Sper	C1 , E1	C1 , E1	C1 , E1	C2 , I2	C1 , I1	-
	ANS to Sper	E1	E1	E1	-	-	-
	ANS to Sn	E1	E1	E1	-	-	-
	Co-A	I1 , E1	I1 , E1	I1 , E1	-	-	-

Table 5.1 The distributions of articles found for cephalometric measurements, classified by 3 surgical techniques (cont.)

	Cephalometric Value	Pre-treatment	Post-treatment	Follow-up	Treatment changes	Relapse changes	Relapse rate
Linear Horizontal Skeletal Measures	A Horizontal	-	-	-	C7 , I1 , E4	C3	-
	ANS Horizontal	-	-	-	C1 , E2	C1	-
	P4	-	-	-	C6	C3	-
	maxilla superimpose	-	-	-	C2	E1	-
Linear Vertical Skeletal Measures	N-A	I1	I1	I1	I1	I1	-
	N-ANS	C3 , I2	C3 , I2	C3 , I1	C2 , I2	C2 , I1	-
	N-Me	E1	E1	E1	-	-	-
	A to FH	C1 , E1	C1 , E1	C1 , E1	C2 , E1	C2 , E1	-
	B to FH	-	-	-	-	-	-
	ANS to FH	C1 , E	C1 , E	C1 , E	C1 , E	C1 , E	-
	PNS to FH	-	-	-	-	-	-
	A to SN-7	E1	E1	E1	I1	I1	-
	ANS to SN-7	E1	E1	E1	-	-	-
	ANS to S horizontal	E2	E2	E2	-	-	-
	Ant.max.alv.ht	I1 , E1	I1 , E1	I1 , E1	I1	I1	-
	A Vertical	-	-	-	C5 , I1 , E3	C3	-
	ANS Vertical	-	-	-	C1 , E1	C1	-
	P4	-	-	-	C6	C3	-
	maxilla superimpose	-	-	-	C1	I1	-

Table 5.1 The distributions of articles found for cephalometric measurements, classified by 3 surgical techniques (cont.)

	Cephalometric Value	Pre-treatment	Post-treatment	Follow-up	Treatment changes	Relapse changes	Relapse rate
Angle Dental Measures	U1 to SN	I1 , E1	I1 , E1	I1 , E1	-	-	-
	U1 to FH	-	-	-	-	-	-
	U1 to PP	C1 , E2	C1 , E2	-	E2	-	-
	U1 to NA	-	-	-	-	-	-
	interincisal angle	-	-	-	-	-	-
Linear Dental Measures	U1 to Nper	-	-	-	-	-	-
	U1 to FH	-	-	-	-	-	-
	Overjet	C1 , I3 , E5	C1 , I3 , E5	C1 , I2 , E4	I2 , E3	I1 , E1	-
	Overbite	C1 , I1 , E3	C1 , I1 , E3	C1 , I1 , E2	I1 , E2	I1 , E1	-
	U1 Horizontal	-	-	-	E1	-	-
	U1 Vertical	-	-	-	E1	-	-
Soft Tissue Measures	Nasolabial angle	C6 , I2 , E3	C6 , I2 , E3	C2 , I2 , E3	C2 , I1 , E1	C1 , I1 , E1	-
	UL to E plane	I2 , E1	I2 , E1	I2 , E1	I1	I1	-
	LL to E plane	I1	I1	I1	I1	I1	-
	N’-Sn-Pg’	I1 , E2	I1 , E2	I1 , E2	-	-	-

C = conventional orthognathic surgery, E= extraoral distraction osteogenesis, I = intraoral distraction osteogenesis

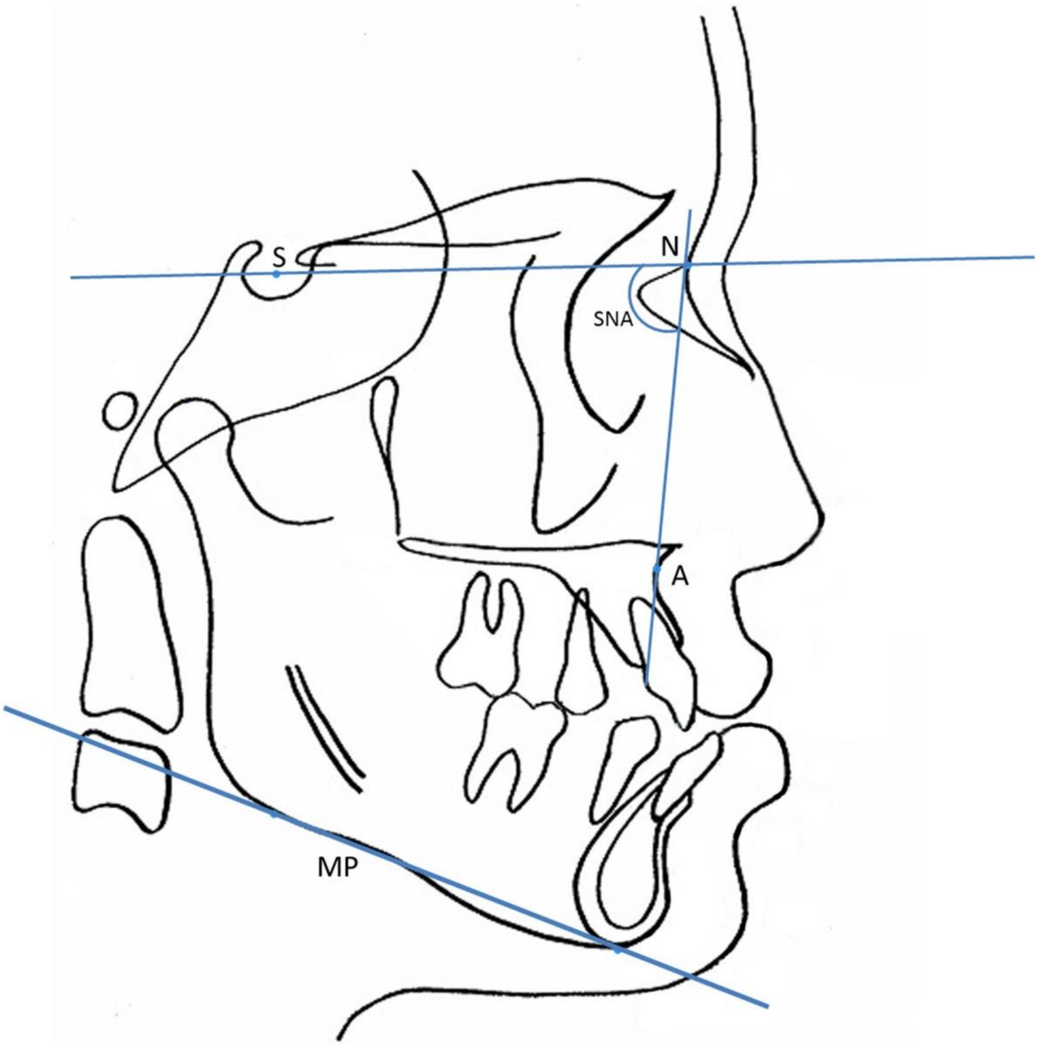

Figure 5.2 Cephalometric landmarks

Using the 6 measurements as criteria (SNA and SN-MP at pre-treatment, post-treatment, and follow-up), the number of final papers eligible for meta-analysis were demonstrated in Table 5.2 as follows; (1) CO (n=9)(Pedersen and Blaho 1975; Ward-Booth, Bhatia et al. 1984; Hochban, Ganss et al. 1993; Posnick and Taylor 1994; Norholt, Sindet-Pedersen et al. 1996; Lisson and Trankmann 1997; Saelen, Tornes et al. 1998; Heliovaara, Ranta et al. 2001; Heliovaara, Ranta et al. 2002), (2) EDO (n= 8)(Figueroa, Polley et al. 2004; Cho and Kyung 2006; Mori, Eguchi et al. 2006; Rachmiel, Aizenbud et al. 2006; Yamauchi, Mitsugi et al. 2006; Minami, Mori et al. 2007; Hashimoto, Otsuka et al. 2008; Gursoy, Hukki et al. 2010), and (3) IDO (n=7)(Gateno, Engel et al. 2005; Rachmiel, Aizenbud et al. 2005; Umstadt 2005;

Wang, Wang et al. 2005; Wenghoefer, Martini et al. 2006; Gulsen, Ozmen et al. 2007; Kahn, Broujerdi et al. 2008). It should be noted that the study by Heliovaara et al. (Heliovaara, Ranta et al. 2002) had two independently sample groups, which were palatal cleft group and bilateral cleft group.

Table 5.2 Characteristics of studies

Study	Technique	Study design	Parameter	n	Age: mean(range)	Follow up	Recalculation	Cleft type	P.flap	ABG	Reliability within study***
Heliovaara 2001	CO	RUCS	1,2,3,4,5,6	40	23.7(16.3-40.4)	1y	-	U	17.5%	82.5%	PEM
Heliovaara 2002/1	CO	RUCS	1,2,3,4,5,6	14	27.2	1y	-	P		20%*	PEM
Heliovaara 2002/2	CO	RUCS	1,2,3,4,5,6	11	23.7	1Y	-	B			
Hochban 1993	CO	RUCS	1,2,3	14	(15-46)	1y	-	U			DF(0.3)
Lisson 1997	CO	CS	1,2,4,5	9	21.83(16-32)		-	B			
Norholt 1996	CO	CS	1,2,3	2		2y	+				
Pedersen 1975	CO	CS	1,2	2	27(22-32)		+	U			
Posnick 1994	CO	RUCS	1,2,3	14	19(17-25)	1y	+	P	57.1%		PEM
Saelen 1998	CO	RUCS	1,2	20	20.0		-	U+B		100%	DF(0.21-0.34)
Ward-Booth 1984	CO	RUCS	1,2,3,4,5,6	13	20.4	2y	-	mix			
Cho 2006	EDO	RUCS	1,2,3	9	(13-19)	1-6y	+	U+B		66.7%	
Figueroa 2004	EDO	RUCS	1,2,3,4,5,6	17	12.6(5.2-23.6)	2y	-	U+B+P			
Gursoy 2010	EDO	RUCS	1,2,3,4,5,6	13	13.3	2y	-	U+B+P			DF(1.2)
Hashimoto 2008	EDO	RUCS	1,2,3,4,5,6	21	16.5(11.0-23.3)	1y	-	U+B			DF(SNA 0.64, SN-MP 0.30)
Minami 2007	EDO	CS	1,2	6	(13-17)		+			100%	
Mori 2006	EDO	CS	1,2	5	19(17-23)		+	U+B	40%	80%	
Rachmiel 2006	EDO	RUCS	1,2,3,4,5,6	18	(11-22)	2y	-	U+B		100%	
Yamauci 2006	EDO	CS	1,2,3,4,5,6	6	(15-18)	1y	-	U+B+P		100%	DF(0.5)

Table 5.2 Characteristics of studies (cont.)

Study	Technique	Study design	Parameter	n	Age: mean(range)	Follow up	Recalculation	Cleft type	P.flap	ABG	Reliability within study
Gateno 2005	IDO	CS	1,2,3,4,5,6	3**	14(12-16)	1y	+	U+B	66.7%		
Gulsen 2007	IDO	CS	1,2,3,4,5,6	4		1y	+				
Kahn 2008	IDO	RUCS	1,2	10	18(14-47)		+	U+B	40%	100%	
Rachmiel 2005	IDO	RUCS	1,2,3,4,5,6	12	(12-18)	1y	-	U+B		100%	
Umstadt 2005	IDO	CS	1,2,3	4	24.5	1.5y	+				
Wang 2005	IDO	RUCS	1,2	10	20.1(13-25)		+	U+B+P		60%	
Wenghoefer 2006	IDO	CS	1,2	3	18.3		+	U+B			

Study design: CS=case series, RUCS=retrospective uncontrolled cohort studies

Parameter: 1=SNA pre-treatment, 2=SNA post-treatment, 3=SNA follow-up, 4=SN-MP pre-treatment, 5=SN-MP post-treatment, 6=SN-MP follow-up

Cleft type: U=unilateral cleft lip and cleft palate, B=bilateral cleft lip and cleft palate, P=cleft palate, mix=unidentified cleft type

P.flap= pharyngeal flap

ABG= alveolar bone graft

* Heliovaara 2002 had two independently sample groups (1=palatal cleft, 2=bilateral cleft)

** stage follow-up, n decreased to 2

*** DF = Dahlberg's formula (in degrees), PEM = partial error of measurement

Characteristics of selected studies are presented in Table 5.2 which included surgical technique, study design, parameters or variables available for analysis, sample size, age (means/range), follow-up period, raw data recalculation using SPSS® program, cleft type, percentage of patients having pharyngeal flap done previously, percentage of patients having secondary alveolar bone graft done, and reliability within study. Minimum age range was 11 years old and maximum was at 47 years old, however, there were a few studies that did not report age. Mixed unilateral, bilateral and palatal cleft types were mostly reported for EDO and IDO group. Minimum percentage of patients having pharyngeal flap was 17.5% and maximum was 66.7%. Minimum percentage of patients having alveolar bone graft prior to surgery was 20% and maximum was 100%.

Regarding risk of bias within study at the outcome level, the error of measurements were performed in 5 articles.(Hochban, Ganss et al. 1993; Saelen, Tornes et al. 1998; Yamauchi, Mitsugi et al. 2006; Hashimoto, Otsuka et al. 2008; Gursoy, Hukki et al. 2010) The precision of the identification of landmarks was tested by double determination methods, separated by at least a 1 week interval, by the same observer. The error of measurements was calculated with the Dahlberg's formula.

$$\text{Error of method}^2 = \sum \boldsymbol{d^2} / \boldsymbol{2n}$$

Where d is the difference between two measurements and n is the number of double determinations. The error calculated ranged from 0.2-0.64 degree in 4 papers indicating very good landmark reproducibility. One paper showed 1.2 degree error for angular measurements.(Gursoy, Hukki et al. 2010)

The partial error of measurements were performed in 3 articles.(Posnick and Taylor 1994; Heliovaara, Ranta et al. 2001; Heliovaara, Ranta et al. 2002) One paper only mentioned that the cephalograms were traced with the reliability within 0.5 mm without the methodology explained.(Posnick and Taylor 1994) Two papers by Heliovaara(Heliovaara, Ranta et al. 2001; Heliovaara, Ranta et al. 2002) mentioned that the computer software used was programmed to calculate the mean of the 2 digitalization which were to be at accuracy of 1 mm.

5.1 SNA

5.1.1 Heterogeneity test (Q value, I Square)

Forest plots of SNA classified by CO, EDO, and IDO group are shown in Figure 5.3. In the diagrams, the point estimate of means is shown as a vertical line and the horizontal line is the 95% CI. The heterogeneity test for CO, EDO, and IDO group (Table 5.3) showed that the Q-values of all variables were statistically significant. The I^2 index of SNA in CO and EDO groups were at high level while in IDO group was at moderate level. Therefore, random effect model were used for estimation of pooled means.

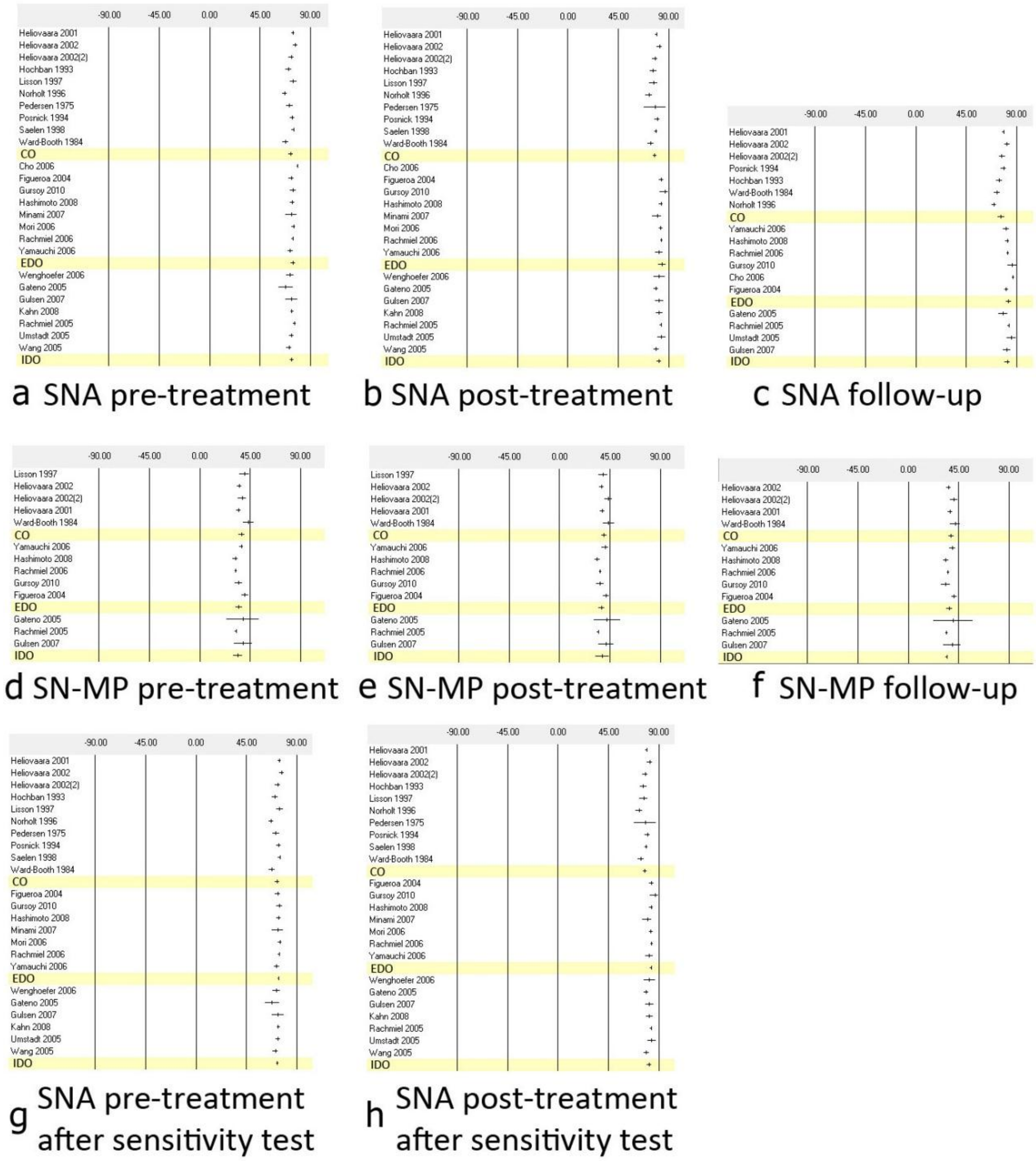

Figure 5.3 Forest plots of variables studied

Table 5.3 Assessment of heterogeneity, publication bias (Egger's test), and sensitivity analysis for SNA and SN-MP in CO, EDO, and IDO techniques

Technique	Parameters	n	N	Heterogeneity test			Egger's regression intercept			Sensitivity analysis		
				Q-value	P value	I^2	Intercept	SE	P value (2-tailed)	Q-value	I^2	n
CO	SNA pre-treatment	9	139	86.366	0.000	89.579	-4.418	3.245	0.211			
	SNA post-treatment	9	139	40.673	0.000	77.872	-2.031	1.460	0.220			
	SNA follow-up	6	108	84.305	0.000	92.883	-3.188	4.581	0.518			
	SN-MP pre-treatment	4	87	14.369	0.006	72.162	4.693	0.801	0.010	NSA	NSA	
	SN-MP post-treatment	4	87	13.621	0.009	70.633	3.681	1.976	0.159			
	SN-MP follow-up	3	78	9.356	0.025	67.933	4.650	1.097	0.051	NSA	NSA	
EDO	SNA pre-treatment	8	95	78.942	0.000	91.133	-4.796	1.341	0.012	7.821	0	9
	SNA post-treatment	8	95	296.564	0.000	97.640	-6.713	3.186	0.080	10.313	32.125	8
	SNA follow-up	6	84	76.079	0.000	93.428	-2.089	3.743	0.607			
	SN-MP pre-treatment	5	75	50.618	0.000	92.098	4.343	2.778	0.216			
	SN-MP post-treatment	5	75	27.480	0.000	85.444	2.012	2.886	0.536			
	SN-MP follow-up	5	75	27.664	0.000	85.541	1.246	2.979	0.704			

Table 5.3 Assessment of heterogeneity, publication bias (Egger's test), and sensitivity analysis for SNA and SN-MP in CO, EDO, and IDO techniques (cont.)

Technique	Parameters	n	N	Heterogeneity test			Egger's regression intercept			Sensitivity analysis		
				Q-value	P value	I^2	Intercept	SE	P value (2-tailed)	Q-value	I^2	n
	SNA pre-treatment	7	46	18.573	0.005	67.696	-2.353	1.057	0.077	11.398	38.586	8
	SNA post-treatment	7	46	22.856	0.001	73.749	-1.536	1.698	0.407			
	SNA follow-up	4	22	7.986	0.046	62.434	-1.184	1.628	0.543			
IDO												
	SN-MP pre-treatment	3	19	2.848	0.241	29.771	1.254	0.407	0.200			
	SN-MP post-treatment	3	19	5.912	0.052	66.172	1.927	0.577	0.185			
	SN-MP follow-up	3	18	1.821	0.402	0.000	1.016	0.344	0.208			

n=number of articles

N=number of subjects

NSA=no significant difference after sensitivity analysis

5.1.2 Estimation of pooled means with 95% confident interval

Table 5.4 demonstrated the results pooled mean estimate from meta-analysis. In CO group, SNA at pre-treatment of patients underwent surgical treatment with conventional orthognathic maxillary advancement showed the pooled mean values of 72.64 degrees (95% CI: 70.63-74.65). The pooled mean value at post-treatment was 77.60 degrees (95% CI: 76.03-79.18). The pooled mean value at follow-up was 76.10 degrees (95% CI: 73.15-79.06).

In EDO group, SNA at pre-treatment of patients underwent surgical treatment with external distraction device showed the pooled mean values of 74.57 degrees (95% CI: 72.56-76.58). The pooled mean value at post-treatment was 84.01 degrees (95% CI: 80.65-87.37). The pooled mean value at follow-up was 83.06 degrees (95% CI: 80.65-85.46).

In IDO group, SNA at pre-treatment of patients underwent surgical treatment with internal distraction device showed the pooled mean values of 73.21 (95% CI: 71.67-74.75). The pooled mean value at post-treatment was 81.33 (95% CI: 79.45-83.21). The pooled mean value at follow-up was 82.14 degrees (95% CI: 79.71-84.57).

Table 5.4 Pooled mean estimate and 95% confident interval

Parameters		SNA					SN-MP				
		n	N	mean	SE	95% CI	n	N	mean	SE	95% CI
CO	pre-treatment	9	139	72.64	1.02	70.63,74.65	4	87	37.77	1.34	35.14,40.40
	post-treatment	9	139	77.60	0.81	76.03,79.18	4	87	39.85	1.24	37.41,42.28
	follow-up	6	108	76.10	1.51	73.15,79.06	3	78	38.52	1.21	36.14,40.90
EDO	pre-treatment	8 9	95	74.57 (74.38)	1.02	72.56,76.58 (73.68,75.08)	5	75	35.14	1.58	32.05,38.23
	post-treatment	8 8	95	84.01 (83.31)	1.72	80.65,87.37 (82.40,84.23)	5	75	37.53	1.37	34.84,40.22
	follow-up	6	84	83.06	1.23	80.65,85.46	5	75	36.83	1.37	34.15,39.51
IDO	pre-treatment	7 8	46	73.21 (73.27)	0.79	71.67,74.75 (71.99,74.55)	3	19	34.18	2.07	30.12,38.24
	post-treatment	7	46	81.33	0.96	79.45,83.21	3	19	38.16	3.03	32.23,44.09
	follow-up	4	22	82.14	1.24	79.71,84.57	3	18	34.55	0.57	33.44,35.66

values in parenthesis = values after sensitivity test

n=number of articles

N=number of subjects

5.1.3 Publication bias (The funnel plots and Egger's test)

The results of funnel plots of all SNA variables in this study, classified by CO, EDO, and IDO are demonstrated in Figure 5.4. Due to aggregation of reported values and small numbers of studies included in the meta-analysis, it was quite difficult to visually inspect asymmetric distribution on the funnel plots. Therefore, detection of bias was also supplemented by the Egger's regression test. Significant *P* values ($P < 0.05$) was shown for SNA pre-treatment in EDO group. However, 2 other variables (SNA post-treatment of EDO group, and SNA pre-treatment of IDO group) were also selected for further sensitivity analysis due to their *P* values proximity to 0.05.

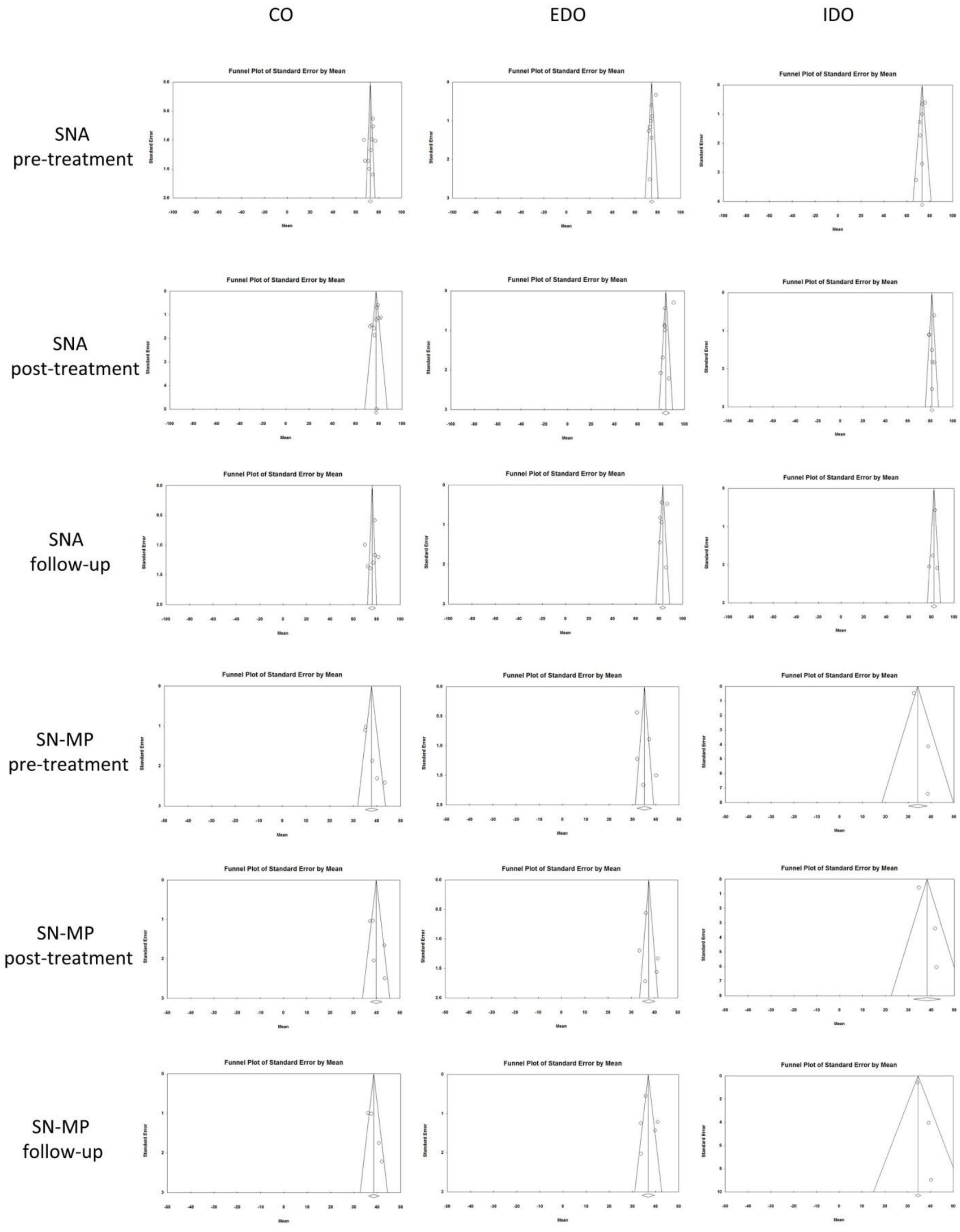

Figure 5.4 Funnel plots of all variables studied

5.1.4 Sensitivity analysis & Trim and fill for pooling means

Using the criteria mentioned in material and methods, 3 variables were selected for further sensitivity analysis as follows. From Table 5.3 of EDO group; (1) SNA pre-treatment (Cho 2006 was excluded), and (2) SNA post-treatment (Cho 2006 was excluded). In IDO group, SNA pre-treatment (Rachmiel 2005 was excluded). Results of corrected funnel plots after trim and fill procedure are presented in Figure 5.5. Solid circles represented hypothetically filled studies of missing data by meta-analysis program, which would need to be included to counterbalance the reported values from genuine studies.

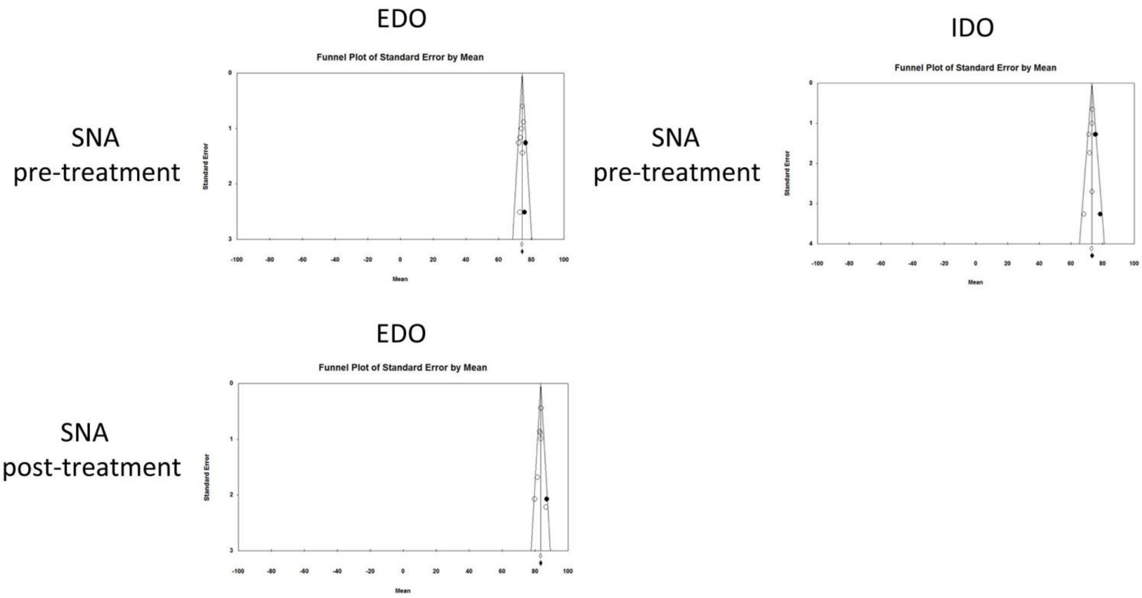

Figure 5.5 Funnel plots of SNA after sensitivity analysis

After the trim and fill, and heterogeneity test was reperformed. Sensitivity analysis results are shown in Table 5.3. Three SNA variables yielded decreased Q values and I^2 index significantly. The I^2 indexes were lowered to the extent of low level for SNA pre-treatment of EDO technique, and to the extent of moderate level for SNA post-treatment of EDO technique and SNA pre-treatment of IDO technique. The funnel plots after the sensitivity analysis are presented in Figure 5.5. The adjusted pooled mean estimate and 95% CI of the following 3 variables: 1) SNA pre-treatment of EDO group, 2) SNA post-treatment of EDO group and 3) SNA pre-treatment of IDO group, are presented in Table 5 (lower row, in parentheses).

5.1.5 The indirect comparison of pooled mean estimates and 95% CI of SNA

Graphs of plotted pooled mean estimate and 95% CI of SNA classified by stages of evaluation (pre-treatment, post-treatment, and follow-up) and surgical techniques (CO, EDO, and IDO) are illustrated in Figure 5.6a.

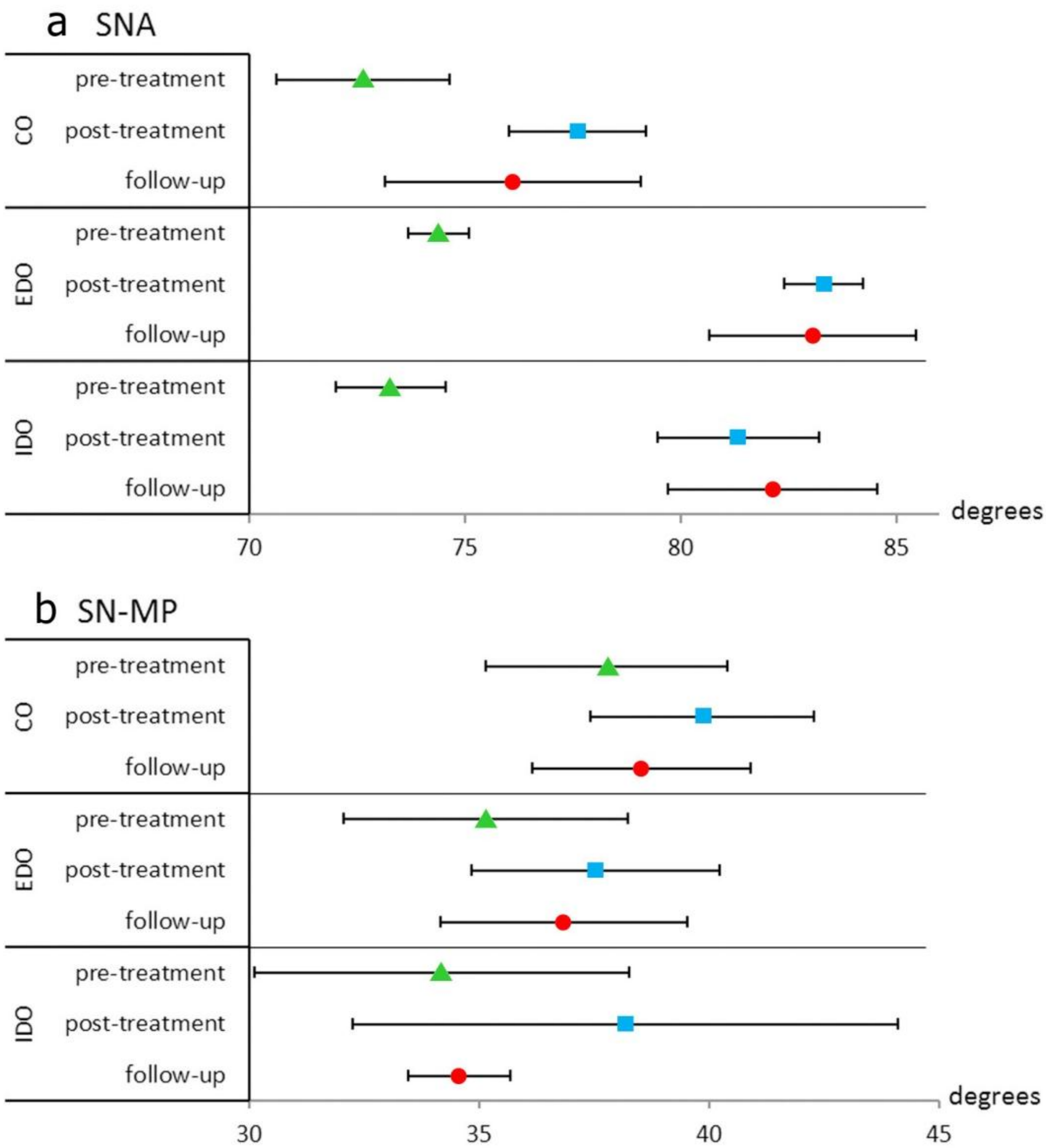

Figure 5.6 Box plots of pooled mean value and 95% CI of SNA and SN-MP classified by surgical techniques and stages in treatment

5.1.5.1 SNA indirect comparison among pre-treatment, post-treatment, and follow-up (Figure 5.6a and Table 5.4)

For SNA in CO group: CO technique could advance the maxilla from pooled mean estimate of 72.64 degrees to post-treatment position of 77.60 degrees. At follow-up, minor relapse happened (76.10 degrees).

For SNA in EDO group: EDO technique could enormously advance the maxilla from pooled mean estimate of 74.38 degrees to post-treatment position of 83.31 degrees. The maxilla position at follow-up (83.06 degrees) was very similar to post-treatment although with greater variation in the follow-up group.

For SNA in IDO group: It could be interpreted that IDO technique could advance the maxilla tremendously from pooled mean estimate of 73.27 degrees to post-treatment position of 81.33 degrees. The maxilla position at follow-up (82.14 degrees) was very similar to post-treatment although with greater variation in follow-up group.

5.1.5.2 SNA indirect comparison among CO, EDO, and IDO (Figure 5.6a and Table 5.4)

5.1.5.2.1 Pre-treatment characteristics

At pre-treatment, the maxillary positions of all groups were considered retrognathic (less than 75 degrees). Due to overlapping of 95% CI and less than 1.5 degrees difference of pooled mean estimate. Pre-treatment SNA (degrees) were similar across 3 groups (CO= 72.64, EDO= 74.38, and IDO= 73.27), which may imply similarity of maxilla position prior to surgery. It should be noted that Maxilla position was most varied in CO group and least varied in EDO group.

5.1.5.2.2 Treatment effect

The maxilla was advanced least in CO group. EDO and IDO could definitely advance the maxilla much greater than CO. At post-treatment, the maxilla could be advanced most or most prognathic with least variation in EDO group (83.31 degrees), followed by IDO group (81.33 degrees), and least in CO group (77.60 degrees). Anyhow, it could not be interpreted that EDO was definitely better than IDO due to overlapping of their 95% CI.

5.1.5.2.3 Follow-up

At average 1-year follow-up, the maxillary position in EDO (83.06 degrees) and IDO group (82.14 degrees) were similar. However, the maxilla position in CO group (76.10 degrees) was more retrognathic.

5.2 SN-MP

5.2.1 Heterogeneity test (Q value, I Square)

Forest plots for CO, EDO, and IDO are shown in Figure 5.3. The heterogeneity test for SN-MP in CO and EDO (Table 5.3), showed that the Q-values of all variables were statistically significant. The I^2 indexes were at moderate to high level. Therefore, random effect model were used and pooled means were estimated. In Table 4, the heterogeneity test for SN-MP in IDO group showed that the Q-values in pre-treatment and follow-up groups were not significant. The I^2 index of SN-MP was low to moderate level (0.0-66.2). In follow-up period, the fixed effect model was used. Otherwise the random effect model were used.

5.2.2 Estimation of pooled means with 95% confident interval

Table 5.4 demonstrated the results of meta-analysis. In CO group, SN-MP at pre-treatment of patients underwent surgical treatment with conventional orthognathic maxillary advancement showed the pooled mean values of 37.77 degrees (95% CI: 35.14-40.40). The pooled mean value at post-treatment was 39.85 degrees (95% CI: 37.41-42.28). The pooled mean value at follow-up was 38.52 degrees (95% CI: 36.14-40.90).

In EDO group, SN-MP at pre-treatment of patients underwent surgical treatment with external distraction device showed the pooled mean values of 35.14 degrees (95% CI: 32.05-38.23). The pooled mean value at post-treatment was 37.53 degrees (95% CI: 34.84-40.22). The pooled mean value at follow-up was 36.83 degrees (95% CI: 34.15-39.51).

In IDO group, SN-MP at pre-treatment of patients underwent surgical treatment with internal distraction device showed the pooled mean values of 34.18 (95% CI: 30.12-38.24). The pooled mean value at post-treatment was 38.16 (95% CI: 32.23-44.09). The pooled mean value at follow-up was 34.55 degrees (95% CI: 33.44-35.66).

5.2.3 Publication bias (The funnel plots and Egger's test)

The results of funnel plots of all 9 variables in this study, classified by CO, EDO, and IDO are demonstrated in Figure 5.4. Significant *P* values (below 0.05) were shown for SN-MP pre-treatment of CO group. However, the other variables (SN-MP follow-up of CO group) were also selected for further sensitivity analysis due to their *P* values proximity to 0.05.

5.2.4 Sensitivity analysis & Trim and fill for pooling means

Using the criteria mentioned in material and methods, two variables were selected for further sensitivity analysis as follows. From Table 5.3 of CO group; (1) SN-MP pre-treatment (Ward-Booth 1984 and/or Lisson 1997 were excluded), and (2) SN-MP follow-up (Ward-Booth 1984 was excluded).

After the trim and fill, and heterogeneity test were reperformed. Sensitivity analysis results are shown in Table 5.3. It should be noted that Q values with their *P* values and I^2 index of 2 variables, which were 1).SN-MP pre-treatment and 2).SN-MP follow-up period, both of CO technique, were not changed to a satisfactory level, no matter what attempts done. Therefore adjusted values would not be used for these variables (indicated as NSA in Table 5.3).

5.2.5 The indirect comparison of pooled mean estimates and 95% CI of SN-MP

Graphs of plotted pooled mean estimate and 95% CI of SN-MP classified by stages of evaluation (pre-treatment, post-treatment, and follow-up) and surgical techniques (CO, EDO, and IDO) are illustrated in Figure 5.6b.

5.2.5.1 SN-MP indirect comparison among pre-treatment, post-treatment, and follow-up (Figure 5.6b and Table 5.4)

For SN-MP in CO group: The mandibular plane steepness was increased, from 37.77 degrees at pre-treatment to 39.85 degrees after surgery. At follow-up the mandibular plane steepness was similar although with tendency toward decrease value (38.52 degrees).

For SN-MP in EDO group: The mandibular plane steepness was slightly increased, from 35.14 degrees at pre-treatment to 37.53 degrees after surgery. At follow-up the mandibular plane steepness (36.83 degrees) was similar to post-treatment.

For SN-MP in IDO group: It could be interpreted that mandibular plane steepness of some patients in this group was increased, from 34.18 degrees at pre-treatment to 38.16 degrees after surgery. Post-treatment variations were remarkably large. At follow-up (34.55 degrees) the mandibular plane steepness decreased back toward pre-treatment value with least variations.

5.2.5.2SN-MP indirect comparison among CO, EDO, and IDO (Figure 5.6b and Table 5.4)

5.2.5.2.1 Pre-treatment characteristics

At pre-treatment, the maxilla-mandible vertical relationships of all groups were within normal range. Due to overlapping of 95% CI and less than 1.5 degrees difference of pooled mean estimate, the pre-treatment SN-MP (degrees) were similar across 3 groups (CO= 37.77, EDO= 35.14, and IDO= 34.18), which imply similarity of maxilla-mandible vertical relationship prior to surgery. SN-MP was most varied in IDO group and least varied in CO group. It should be noted that SN-MP in CO group showed greater tendency toward hyperdivergent skeletal than EDO and IDO.

5.2.5.2.2 Treatment effect

All 3 groups demonstrated the increase of mandibular plane steepness after surgery (CO= 39.85, EDO= 37.53, and IDO= 38.16). The CO group showed strikingly greater amount of change in mandibular plane after surgery compared to the other 2 groups. Generally, the maxilla-mandible vertical relationship were quite similar at post-treatment. However, IDO at post-treatment showed greatest variation with the farthest extent toward the upper and lower limits.

5.1.5.2.3 Follow-up

At average 1 year follow-up, the mandibular plane steepness of all groups showed tendency to rotated toward pre-treatment values. Although the CO (38.52 degrees) and EDO (36.83 degrees) showed similar mandibular plane steepness, the CO group showed greater tendency toward hyperdivergent skeletal. It should be noted that IDO showed much less mandibular plane steepness (34.55 degrees) than CO group (38.52 degrees), with least variation of values than the other 2 groups.

5.3 Subgroup analysis

Subgroup analysis could not be performed for variables of interest as previously planned (age, cleft type, pharyngeal flap, and alveolar bone graft). After detailed examining the papers, it was found that the number of studies were inadequate. The reasons were due to the fact that most papers would report the percentage of patients who presented with variables of interest. Besides, majority of papers did not directly compare or report the cephalometric values classified by the variables mentioned above. Information of age could not be used because age range or means were reported without standard deviation.

5.4 Calculation for treatment change, relapse change, and relapse rate

The calculated treatment change, relapse change, and relapse rate are shown in Table 5.5. The results of estimate relapse rate for SNA in CO was -30.24%, EDO was -2.80%, and follow-up advanced rate of IDO was +10.05%. The estimate results of SN-MP relapse rate for CO was -63.94%, EDO -29.29%, and IDO -90.70%.

Table 5.5 Relapse rate of each techniques

Group	Amount of treatment change after surgery (degree)	Amount of relapse (degree)	Relapse rate (%)
SNA*			
CO	+4.96	-1.5	-30.24
EDO	+8.93	-0.25	-2.80
IDO	+8.06	+0.81	+10.05
SN-MP**			
CO	+2.08	-1.33	-63.94
EDO	+2.39	-0.7	-29.29
IDO	+3.98	-3.61	-90.70

* Advance maxilla = +

** Increase mandibular plane = +

CHAPTER VI
DISCUSSION

So far, there has been no study reported on comparison of effectiveness and stability across the 3 surgical techniques for cleft patient, namely CO, EDO, and IDO. In our study, the indirect comparison of SNA and SN-MP among 3 surgical techniques for cleft patients, using pooled mean estimate from meta-analysis indicated that at pre-treatment the maxillary positions were in severe retrognathic and the mandibular plane were in normal range for all 3 groups. According to the calculation of pooled mean estimate in Table 5, after surgical treatment, the maxillary position of CO group was advanced +4.96 degrees which was almost half less than the EDO (+8.93 degrees) and the IDO groups(+8.06 degrees). At 1 year follow-up, the maxilla position (SNA) in conventional orthognathic surgery was still considered retruded, while maxilla in EDO and IDO were maintained well in normal position (SNA in degrees: CO=76.10, EDO=83.06, and IDO=82.14). The CO showed more relapse rate than EDO and IDO (-30.24%, -2.80% and +10.05% respectively). Our findings explored the greater effectiveness and better 1-year stability of EDO and IDO than the CO. Interestingly, the effectiveness and stability of EDO and IDO were quite similar. Regarding the mandibular vertical position after surgery, the mandibular plane rotated downward-backward in all 3 groups. The mandibular plane increase was +2.08, +2.39 and +3.98 degrees for CO, EDO, and IDO respectively. Fortunately, at average of 1 year follow-up periods, the mandibular plane tended to reverse toward their original conditions in all groups. The mandibular plane of IDO group showed greatest relapse rate of -90.70%, followed by CO of -63.94% and IDO of -29.29% respectively.

The strength of evidence based on SNA was strong and could be considered relevant to oral surgeons. However, due to small numbers of articles, the strength of evidence based on SN-MP may not be solid.

The strength of this study was related to the use of meta-analysis statistics to overcome the problems of lacking the comparative research comprising CO, EDO and IDO in literatures. The pooled mean estimate from meta-analysis had made it possible to perform indirect comparison among the 3 surgical techniques. The indirect meta-analysis used in this study allowed the possibility to compare the differences among the 3 surgical techniques. In addition, we proposed a hypothetical calculation for treatment change, relapse change, and relapse rate using the pooled mean estimate, eventhough these values were insufficient or had never been reported previously. (Table 2) Attempts were also made in our study to identify publication bias. Sensitivity analysis was performed in order to estimate the adjusted pooled means. Moreover, the indirect comparison of SNA and SN-MP, using pooled mean estimate from meta-analysis, indicated that maxillary position and mandibular plane steepness at pre-treatment were not different among the 3 groups. The homogeneity of pre-treatment characteristics was advantageous for evaluation of treatment changes. The pre-treatment SNA and SN-MP values were similar to those reported by Rachmiel et al (Rachmiel, Aizenbud et al. 2005) for IDO and Yamauchi et al(Yamauchi, Mitsugi et al. 2006) for EDO.

6.1 Post-treatment results/Treatment change

6.1.1 SNA

Our results showed that EDO and IDO could advance the maxilla and increase the SNA angle almost twice as much as CO. For CO, the result of our study confirmed previous reports that conventional orthognathic surgery often fall short of achieving adequate maxilla advancement.(Freihofer 1977; Hochban, Ganss et al. 1993; Erbe, Stoelinga et al. 1996; Heliovaara, Ranta et al. 2002) The maxilla in cleft patients was often difficult to mobilize because of the scarring from primary surgery and/or revision. Scar in soft tissue of palate and upper lip in cleft patients could create difficulties in the advancement of the maxilla beyond 6 mm.(Bevilacqua, Ritoli et al. 2008) On the contrary, EDO and IDO were more capable of taking the maxilla forward to the normal position after surgery (SNA in degrees: CO=77.60, EDO=83.31, and IDO=81.33). For EDO, our finding of 8.93 degrees of estimated treatment change of SNA after surgery (Table 6) was also in agreement with Yamauchi et al(Yamauchi, Mitsugi et al. 2006), who reported in his study that the post-treatment results and treatment change of SNA angle increased from 72.38 to 81.48 degrees, and the ANB angle increased by 11.08 immediately after removing the distraction device. Our estimate values was also comparable to the range reported by Polley et al(Polley and Figueroa 1998), found that, patients who used rigid external device can increase SNA angle 7.7 degrees. However, the treatment change in our study was less than that reported by Figueroa et al(Figueroa, Polley et al. 2004) who performed the first long-term study over 3 years on maxillary advancement using rigid external distractors (RED) in 17 patients with CLP. They reported SNA angle increase of 10.2 degrees after distraction. The reason might be due to the greater severity of maxillary hypoplasia and over-correction in Figueroa et al's study.(Figueroa, Polley et al. 2004)

On the contrary, our results did not support the findings by Chua et al(Chua, Hagg et al. 2010) who reported mean horizontal movement A point in IDO group was at 7.04 mm., while in CO was at 6.84 mm. which was considered clinically insignificant between the two groups. The reason could be due to fact that many of those subjects in Chua's study underwent 2 jaws surgery and the characteristics of their subjects which were moderate cases.

6.1.2 SN-MP

From our study, increase in vertical dimension SN to mandibular plane angle after surgery found in all 3 groups was probably due to slight downward movement of the maxilla, resulting in a more clockwise rotation or posterior position of the mandible which could partly help improving the skeletal class III relationship. The other reason for increase in vertical dimension may be related to the type of osteotomy for maxilla. Generally, the maxillary osteotomies performed could be; (a) horizontal osteotomy—for forward distraction of the maxilla, (b) The step osteotomy is performed in children where the canine or premolar roots or buds are in higher position in the maxilla, and (c) oblique osteotomy—for forward and downward distraction.(Rachmiel, Aizenbud et al. 2005) The latter type could cause increase of mandibular plane with slight vertical elongation.

The greatest increase of mandibular plane steepness after surgery was found in CO group. One of the factors could be due to significant downward movement of maxilla in combination with maxillary advancement in order to correct 3 dimensional maxillary hypoplasia. While surgical clockwise rotation of maxilla-mandibular complex was helpful to reduce concavity profile especially in patient with short chin-throat length, it could be another cause of increased mandibular plane. In EDO and IDO groups, the occlusal interference during maxilla distraction could contribute to the situation. Our study found mandibular plane increase after EDO of 2.39 degrees which was similar to Yamauchi et al(Yamauchi, Mitsugi et al. 2006) who reported that the mandibular plane line (SN/MP) angle was increased 3.78 degrees with a slight clockwise rotation.

Interestingly, mandibular plane rotated greatest with largest variation in IDO group at post distraction treatment. Our results supported the findings by Rachmiel et al(Rachmiel, Aizenbud et al. 2005) who reported that 5 of the 12 patients showed a tendency to open bite that was resolved by interocclusal elastics placement during the consolidation period. In our opinion, the vector of elongation of the intraoral devices was also determined by the osteotomy pattern and the direction of placing the device which could hardly be manipulated by the surgeon during distraction. Intraoral distractor placement site was located in the posterior maxilla. The devices were usually positioned with an upper anchorage on the zygomatic buttresses where the bone is thickest. The lower arm of the maxillary device was anchored along the lateral maxillary wall below the transverse osteotomy and above the tooth apexes. Due to this anatomical constraint, if vector of activation created downward movement of posterior maxilla, it could lead to occlusal interference and force the mandible to rotate downward and backward. Fortunately, the mandibular plane in IDO group was recovered back toward its original position at 1 year follow-up.(Rachmiel, Potparic et al. 1993)

6.2 Follow-up

The reason for choosing 1 year follow-up in our study was based on previous report(Chua, Hagg et al. 2010) that significant relapse occurring within the first postoperative year.

6.2.1 SNA

A greater tendency to relapse in cleft patients compared to non-cleft patients was found in conventional orthognathic surgery. Relapse of maxilla in horizontally backward direction can cause class III malocclusion, increased upper incisor angulation and/or increased retroclination of lower incisors to compensate for skeletal relapse. Despite overcorrection and/or the use of bone grafts and rigid fixation, postsurgical relapse of approximately 4 to 40 percent has been reported by Bevilacqua et al(Bevilacqua, Ritoli et al. 2008), Thongdee et al(Thongdee and Samman 2005)(25%-50%), and Chua et al(Chua, Hagg et al. 2010)(37%). The results of our estimated relapse rate for SNA in CO (-30.24%) was in agreement with those previous reports.

For EDO, our result showed pooled mean estimate of relapse of SNA of 0.25 degrees which was in agreement with Yamauchi et al(Yamauchi, Mitsugi et al. 2006) who reported that the SNA angle had decreased by 0.88 degrees after 1 year. The amount of maxilla relapse in backward direction was much greater in CO group compared to EDO and IDO group which were in agreement with other distraction osteogenesis studies. (Polley and Figueroa 1998; Figueroa, Polley et al. 2004; Rachmiel, Aizenbud et al. 2005)

Our results of estimate relapse rate for SNA (CO: -30.24% versus EDO: -2.80%) indicated that EDO was more stable compared to CO which supported previous findings.(Polley and Figueroa 1998; Figueroa, Polley et al. 2004; Rachmiel, Aizenbud et al. 2005) The relapse rate of the CO group was higher than the IDO group (CO: -30.24% versus IDO: +10.05%) also supported previous reports.(Cheung, Chua et al. 2006; Chua, Hagg et al. 2010) The reasons for the significant maxilla advancement and smaller relapse in EDO and IDO when compared with CO, was likely related to the gradual surgical movement of the maxilla, which causes less counterforce to pull the maxilla back to the original position.(Polley and Figueroa 1998; Figueroa, Polley et al. 2004; Rachmiel, Aizenbud et al. 2005)

So far, there has been no study comparing relapse between EDO and IDO. For EDO, Figueroa et al(Figueroa, Polley et al. 2004) performed the first long-term study over 3 years on maxillary advancement using rigid external distractors (RED) in 17 patients with CLP. They reported 23.5% relapse during the postoperative period.

For IDO, Rachmiel et al (Rachmiel, Aizenbud et al. 2005) in a long-term study of cleft maxillary hypoplasia, found a relapse rate of only 7.32% after 2 years with the use of internal distractors. These information may lead some clinicians to believe that IDO was more stable or showing less relapse than EDO.(Chua, Hagg et al. 2010) However, our data suggested that maxilla positioned in EDO and IDO were equally maintained well during 1- year follow-up.

Interestingly, for IDO, Chua et al(Chua, Hagg et al. 2010)reported the forward movement of maxilla during follow-up instead of relapse. In their RCT study, they found that in the CO group, the maxilla relapsed backward and upward. Whereas in the DO group, it advanced more forward and downward over 12 weeks(Cheung, Chua et al. 2006) and long term 5 years follow-up(Chua, Hagg et al. 2010). Our relapse rate of + 10.05% was much lower than Chua et al(Chua, Hagg et al. 2010), who showed that at 1-2 years follow-up, IDO showed horizontal movement A point forward 2.48 mm (+35.22%) while CO showed horizontal movement A point backward (relapse) -1.57 mm (backward 11.26%). In addition, due to overlapping of 95%CI, our results showed that the relapse amount and the position of maxilla at 1 year follow-up were quite similar between EDO and IDO. Besides, the amount of SNA change during 1 year follow-up may be considered clinically insignificant (SNA at post-treatment=81.33, and follow-up=82.14) (Figure 11a). Although maxilla showed tendency toward slight advancement with follow-up advanced rate, it was still too early to confirm the findings of Chua et al.(Chua, Hagg et al. 2010) The reasons were due to small numbers of papers and the superimposed effect of intermaxillary elastics used during post-distraction orthodontics. Therefore, more studies are needed to confirm this notion.

Our study was also in disagreement with Beak et al(Baek, Lee et al. 2007), who studied the difference between CO and EDO and found that, there was not significant different of relapse in anteroposterior position of maxilla. They reported the average amount of relapse in the CO and EDO groups of 24% and 21% respectively and concluded that the use of the RED device did not bring any advantage in significantly reducing the relapse rate. Anyhow, the true extent of relapse in the study reported by Baek et al(Baek, Lee et al. 2007) was unpredictable, as 45.5% of the samples were young patients with incomplete mandibular growth. Therefore, it was difficult to separate the long-term changes of the maxillary position resulting in surgical relapse from those of facial growth. In addition, if distraction is performed during the growth period, relapse can be exaggerated as a result of continuing mandibular growth.

6.2.2 SN-MP

There were limited numbers of studies reporting follow-up change of SN-MP. At 1 year follow-up, the SN-MP angle in EDO group rotated counterclockwise by 0.7 degrees which was similar to Yamauchi et al(Yamauchi, Mitsugi et al. 2006)who reported the mean decrease of 1.18 degrees. This was probably due to point A moving superiorly and posteriorly. Relapse of maxilla in vertically upward direction may create loss of incisal shown at rest and reduced anterior lower facial height. Chua et al(Chua, Hagg et al. 2010) showed that at 5 years follow-up: CO group had U1 to SN increase of 10 degrees while IDO group showed only 0.7 degrees increase. It should be noted that the largest relapse rate in IDO of -90.70% was probably associated with its largest variation of SN-MP values after surgery.

6.3 Limitations

Some limitations of this study were present which may reduce the validity of our results to some extent. Ideally, in order to compare the treatment effect of 3 techniques, the data should have been a randomized control trial that compare among the 3 techniques. Because of the insufficient numbers of patient, the variety of techniques of surgery, the patient's cleft type, the variety of protocols for treating cleft patients in different center, the severity of facial deformities of patients, and the availability of distraction devices, there was no RCT study ever published to compare these three types of surgery. Secondly, we had found that there were too much variation of cephalometric measurements used in each study, making it difficult to collect enough papers for inclusion of any cephalometric of interest in meta-analysis statistics. Thirdly, the numbers of articles for SN-MP were marginal which was too closed to the minimum numbers accepted for meta-analysis. Because of this reason, the computation using sensitivity analysis was not helpful to eradicate publication bias, especially for the SN-MP pre-treatment and SN-MP follow-up period, both of CO technique. Therefore, their validity may be questioned and the results associated with SN-MP should be interpreted with extreme cautions.

Apart from surgical techniques (CO, EDO, and IDO) mentioned in our study, there were other factors which may be implicated in treatment change and relapse in cleft patients, such as the severity of maxillary deficiency, severity of occlusal disharmony, type of cleft, scarring from previous surgery of the lip, alveolus, and palate, presence of pharyngeal flap, of alveolar cleft and age.(Hochban, Ganss et al. 1993; Harada, Sato et al. 2004; Rachmiel 2007; Chua, Hagg et al. 2010) In children receiving DO, there were reports of some follow-up growth from the distracted maxilla. The maxillary growth was in an inferior direction and the mandibular growth would continue in the anteroposterior direction. Unfortunately, the subgroup analysis could not be performed to evaluate these factors due to insufficient numbers of papers.

Besides the issue of effectiveness and stability, there were other factors considered for surgical technique selection. According to Rachmiel et al(Rachmiel, Aizenbud et al. 2005), the main advantage of the maxillary internal devices was that the device was located under the soft tissue and was socially preferred by the patients. Disadvantages were; (1) the devices cannot perform three-dimensional corrections, (2) less control of vector of lengthening in relation to the extraoral devices, (3) limited distraction length, (4) infection of the oral mucosa due to the prolonged retention of the distractors, and (5) a second operation for removal was required. With the extraoral devices, there was better control of vector of lengthening, the vector can be changed during lengthening with longer distraction length than the intraoral distractors, and the removal of the device was performed simply by unscrewing the fixation screws.(Cheung and Chua 2006; Cheung, Chua et al. 2006) Therefore, the selection of appropriate surgical technique for each CLP patient may depend largely on surgeon’s judgment.

This meta-analysis provided a preliminary evidence-based data to oral surgeon and orthodontist to assist in choosing surgical technique for cleft patients. This study explored that the effectiveness and stability of both EDO and IDO was much better than CO. It added to new information to the existing literature that clinical effectiveness and stability between EDO and IDO were similar. Our results may imply that clinicians and patients should be aware of limited amount of advancing the maxilla when using CO technique. Besides the maxilla in CO technique after orthognathic surgery still remained in retrognathic position with risk of higher relapse than EDO and IDO. Because of these reasons, CO may not be an appropriate technique to be used solely for moderate to severe maxillary retrognathic CLP cases. These limitations may force the clinicians to plan treatment with extraction or anterior subapical osteotomy in the lower arch or masking the maxillary deformity with 2 jaws surgery using mandibular setback osteotomies even for normally positioned mandibles. In order to normalize the maxilla position, EDO or IDO should be considered as treatment of choice.

Clinicians may encounter a tendency of skeletal openbite in all 3 techniques, therefore, cautions should be exercised especially in case with existing skeletal openbite at pre-treatment. These vertical changes could also lead to an increased lower facial height. In case of anterior open-bite was detected during distraction with EDO or IDO, additional anterior box elastics were recommended to guide the final vector of lengthening and proper occlusion

In the future, more RCT studies are yet needed to directly compare treatment results, and follow-up changes of the 3 types of surgical techniques. Due to scarcity of published comparative papers at present, suggestions for future clinical studies may involve the collaborative multi-center studies which are necessary to overcome the problem of sample sizes. Craniofacial centers may develop universal protocol, using similar cephalometric measurements. Developing centralized web-based application for systematic records keeping will be of great assistance in the future.

CHAPTER VII
CONCLUSIONS

1. For SNA, our findings showed EDO and IDO might advance the maxilla greater than CO. Normalization of sagittal maxillary position relation was achieved using EDO and IDO, while the maxilla in CO group remained retrognathic.

2. For SNA, EDO and IDO group showed 1-year stability might better than CO.

3. For SNA, the amount of advancement and stability of EDO and IDO were quite similar.

4. After surgery, the mandibular plane rotated downward-backward in all 3 groups. Fortunately, at 1 year follow-up period, the mandibular plane tended to reverse toward their original conditions in all groups.

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APPENDICES

APPENDIX A
EXAMPLE OF THE ELECTRONIC DATABASES SEARCHED AND THE SEARCH STRATEGY USED IN THE META-ANALYSIS (as of April 15, 2010)

Databases of Published Trials	Search Strategy Used	Hits
Medline	(cleft) and (maxilla or maxillary) and (osteotomy or distraction or advancement or orthognathic surgery) and (measurement or cephalometry or cephalometric or analysis or cephalograph or cephalographs)	187
ISI Web of Science	Topic=((cleft) and (maxilla or maxillary) and (osteotomy or distraction or advancement or orthognathic surgery) and (measurement or cephalometry or cephalometric or analysis or cephalograph or cephalographs)) Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI. Lemmatization=On	71
Scopus	TITLE-ABS-KEY((cleft) AND (maxilla OR maxillary) AND (osteotomy OR distraction OR advancement OR orthognathic surgery) AND (measurement OR cephalometry OR cephalometric OR analysis OR cephalograph OR cephalographs))	133

APPENDIX B
STANDARDIZED DATA EXTRACTION FORM

Title				
Authors				
Journal		**Years :**	**Vol :**	**Pages :**

Part A: Methodological Characteristics

<u>Inclusion criteria</u>

- Randomized controlled clinical trials (RCTs)
- Prospective controlled clinical trials (CCTs)
- Retrospective controlled cohort studies
- Retrospective uncontrolled cohort studies
- Case series
- Case report ≥ 2 cases

<u>Exclusion criteria</u>

- Non-English publication
- Animal research
- Commentary / Review article / Systematic review/ 1 case report
- Statistical technique problems (e.g. no SD, no Mean, report Median or Mode or Quartile)
- Insufficient data (Repeated samples by multiple publication, Repeated abstract from same paper, Thesis that found published paper)

<u>Ineligibility criteria</u>

- Characteristics of patient not associated

  e.g. Non-cleft sample / Infant, Toddler / Not maxillary hypoplasia / Class II skeletal discrepancy / Bimaxillary protrusion, Maxillary protrusion / Mandibular prognathism / Severe facial cleft

- Treatment strategies not associated

  e.g. Primary surgery such as lip repair, palate closure, primary bone graft / Mandibular surgery or distraction / Transverse distraction / Contraction osteogenesis / Sleep apnea treatment or airway management / Correction for maxillary prognathism / Premaxillary setback or intrusion / Alveolar bone graft /Soft tissue plastic surgery / Lefort III surgery or monobloc or facial bipartition

- Treatment outcome not associated

  e.g. Plastic surgery or esthetic outcome / Speech outcome without lateral cephalometry

- Research methodology not associated

  e.g. Finite element / Computer program for surgical prediction

Part B: Design Characteristics

<table>
<tr><td>Control group</td><td colspan="3">Δ Yes</td><td colspan="3">Δ No</td></tr>
<tr><td>Racial</td><td>Δ Asian</td><td>Δ Caucasian</td><td>Δ African</td><td>Δ Hispanic</td><td>Δ Arabian</td><td>Δ Unidentified</td></tr>
<tr><td>Type of outcomes</td><td colspan="2">Δ raw data</td><td colspan="2">Δ continuous data</td><td colspan="2">Δ mixed</td></tr>
<tr><td>n =</td><td colspan="6">Gender Δ (M= ,F=), Δ Unidentified ( )</td></tr>
<tr><td rowspan="6">Finding</td><td colspan="6">1.</td></tr>
<tr><td colspan="6">2.</td></tr>
<tr><td colspan="6">3.</td></tr>
<tr><td colspan="6">4.</td></tr>
<tr><td colspan="6">5.</td></tr>
<tr><td colspan="6">6.</td></tr>
<tr><td>Type of Surgery</td><td>Δ CO</td><td>Δ EDO</td><td>Δ IDO</td><td colspan="3">Appliance ( )</td></tr>
<tr><td>Latency=</td><td>Activation=</td><td>Rate=</td><td>Consolidation=</td><td colspan="3">F/U period=</td></tr>
<tr><td>Δ Pre-treatment</td><td>Δ Post-treatment</td><td>Δ Follow-up</td><td>Δ Treatment change</td><td>Δ Relapse change</td><td colspan="2">Δ Relapse rate</td></tr>
</table>

Subgroup: ……………………………………………………..………...………………

Side effect: ………………………………………………………..…..…………………….

Complication: ………………………………………………………………………………...

Others: ……………………………………………………………………..………………

Part C: Cephalometric measurement

	Cephalometric Value	Pre-treatment	Post-treatment	Follow-up	Treatment changes	Relapse changes	Relapse rate
Angle Skeletal Measures	SNA						
	SNB						
	ANB						
	FH-PP						
	FH-FO						
	FH-MP						
	SN-PP						
	SN-FO						
	SN-MP						
	MP-PP						
	NAPg						
	SNPg						
	LFH ratio						
Linear Horizontal Skeletal Measures	AO-BO						
	A to Nper						
	B to Nper						
	ANS to Nper						
	PNS to Nper						
	A to Sper						
	ANS to Sper						
	ANS to Sn						
	Co-A						
	A Horizontal						
	ANS Horizontal						
	P4						
	maxilla superimpose						
Linear Vertical Skeletal Measures	N-A						
	N-ANS						
	N-Me						
	A to FH						
	B to FH						
	ANS to FH						
	PNS to FH						
	A to SN-7						
	ANS to SN-7						
	ANS to S horizontal						
	Ant.max.alv.ht						

	A Vertical						
	ANS Vertical						
	P4						
	maxilla superimpose						
Angle Dental Measures	**U1 to SN**						
	U1 to FH						
	U1 to PP						
	U1 to NA						
	interincisal angle						
Linear Dental Measures	**U1 to Nper**						
	U1 to FH						
	Overjet						
	Overbite						
	U1 Horizontal						
	U1 Vertical						
Soft Tissue Measures	**Nasolabial angle**						
	UL to E plane						
	LL to E plane						
	N’-Sn-Pg’						

APPENDIX C

RISK OF BIAS ASSESSMENT CRITERIA

Risk of bias	Interpretation	Within study
Low risk of bias	Plausible bias unlikely to seriously alter the result	Performed the error of measurement e.g. Dahlberg’s formula
Unclear risk of bias	Plausible bias that raises some doubt about the result	Unclear (partial) process of the error of measurement
High risk of bias	Plausible bias that seriously weakens confidence in the results	Not describe process of the error of measurement

APPENDIX D
RAW DATA: MEAN AND SD OF STUDIES

SNA Pre-treatment

Study name	Subgroup within study	Mean	Standard deviation	Sample size	Standard error
Heliovaara 2001	co	74.900	4.000	40	0.632
Heliovaara 2002 P	co	77.000	3.800	14	1.016
Heliovaara 2002 B	co	73.000	3.900	11	1.176
Hochban 1993	co	70.900	5.100	14	1.363
Lisson 1997	co	74.890	4.790	9	1.597
Norholt 1996	co	67.000	1.410	2	0.997
Pedersen 1975	co	71.500	2.120	2	1.499
Posnick 1994	co	73.710	3.700	14	0.989
Saelen 1998	co	75.050	3.430	20	0.767
Ward-Booth 1984	co	67.900	4.900	13	1.359
Cho 2006	edo	78.500	1.000	9	0.333
Figueroa 2004	edo	73.200	4.800	17	1.164
Gursoy 2010	edo	74.600	5.200	13	1.442
Hashimoto 2008	edo	74.100	4.600	21	1.004
Minami 2007	edo	73.000	6.160	6	2.515
Mori 2006	edo	75.100	1.980	5	0.885
Rachmiel 2006	edo	74.420	2.540	18	0.599
Yamauchi 2006	edo	72.300	3.090	6	1.261
Wenghoefer 2006	ido	71.830	3.010	3	1.738
Gateno 2005	ido	68.230	5.650	3	3.262
Gulsen 2007	ido	73.380	5.410	4	2.705
Kahn 2008	ido	73.600	2.070	10	0.655
Rachmiel 2005	ido	75.750	2.090	12	0.603
Umstadt 2005	ido	73.350	2.010	4	1.005
Wang 2005	ido	71.250	4.040	10	1.278

SNA Post-treatment

Study name	Subgroup within study	Mean	Standard deviation	Sample size	Standard error
Heliovaara 2001	co	79.100	3.700	40	0.585
Heliovaara 2002 P	co	81.800	4.200	14	1.122
Heliovaara 2002 B	co	77.800	4.000	11	1.206
Hochban 1993	co	76.100	5.900	14	1.577
Lisson 1997	co	76.380	5.600	9	1.867
Norholt 1996	co	72.500	2.120	2	1.499
Pedersen 1975	co	78.000	7.070	2	4.999
Posnick 1994	co	79.890	4.280	14	1.144
Saelen 1998	co	78.550	3.130	20	0.700
Ward-Booth 1984	co	74.000	5.200	13	1.442
Cho 2006	edo	90.730	0.880	9	0.293
Figueroa 2004	edo	83.400	4.100	17	0.994
Gursoy 2010	edo	86.600	8.000	13	2.219
Hashimoto 2008	edo	83.200	4.100	21	0.895
Minami 2007	edo	79.750	5.080	6	2.074
Mori 2006	edo	82.800	1.920	5	0.859
Rachmiel 2006	edo	83.580	1.880	18	0.443
Yamauchi 2006	edo	81.400	4.120	6	1.682
Wenghoefer 2006	ido	81.530	4.390	3	2.535
Gateno 2005	ido	78.800	1.900	3	1.097
Gulsen 2007	ido	81.630	3.640	4	1.820
Kahn 2008	ido	81.500	4.770	10	1.508
Rachmiel 2005	ido	83.500	2.070	12	0.598
Umstadt 2005	ido	83.800	3.670	4	1.835
Wang 2005	ido	79.050	3.530	10	1.116

SNA Follow-up

Study name	Subgroup within study	Mean	Standard deviation	Sample size	Standard error
Heliovaara 2001	co	78.400	3.700	40	0.585
Heliovaara 2002 P	co	81.500	4.500	14	1.203
Heliovaara 2002 B	co	77.000	4.300	11	1.296
Posnick 1994	co	78.600	4.370	14	1.168
Hochban 1993	co	74.700	5.200	14	1.390
Ward-Booth 1984	co	72.400	4.900	13	1.359
Norholt 1996	co	70.000	1.410	2	0.997
Yamauchi 2006	edo	80.600	3.540	6	1.445
Hashimoto 2008	edo	82.000	4.300	21	0.938
Rachmiel 2006	edo	82.250	1.860	18	0.438
Gursoy 2010	edo	85.900	7.500	13	2.080
Cho 2006	edo	86.890	1.420	9	0.473
Figueroa 2004	edo	81.000	3.400	17	0.825
Gateno 2005	ido	78.050	2.900	2	2.051
Rachmiel 2005	ido	83.170	1.990	12	0.574
Umstadt 2005	ido	85.300	4.180	4	2.090
Gulsen 2007	ido	81.250	3.520	4	1.760

SN-MP Pre-treatment

Study name	Subgroup within study	Mean	Standard deviation	Sample size	Standard error
Lisson 1997	co	40.120	6.920	9	2.307
Heliovaara 2002 P	co	35.300	3.800	14	1.016
Heliovaara 2002 B	co	38.100	6.200	11	1.869
Heliovaara 2001	co	35.100	7.000	40	1.107
Ward-Booth 1984	co	43.400	8.700	13	2.413
Yamauchi 2006	edo	37.200	2.180	6	0.890
Hashimoto 2008	edo	32.100	5.600	21	1.222
Rachmiel 2006	edo	32.000	1.860	18	0.438
Gursoy 2010	edo	34.700	6.000	13	1.664
Figueroa 2004	edo	40.200	6.200	17	1.504
Gateno 2005	ido	38.630	12.810	3	7.396
Rachmiel 2005	ido	32.580	1.620	12	0.468
Gulsen 2007	ido	38.750	8.270	4	4.135

SN-MP Post-treatment

Study name	Subgroup within study	Mean	Standard deviation	Sample size	Standard error
Lisson 1997	co	38.810	6.120	9	2.040
Heliovaara 2002 P	co	37.200	3.900	14	1.042
Heliovaara 2002 B	co	43.400	5.500	11	1.658
Heliovaara 2001	co	38.400	6.500	40	1.028
Ward-Booth 1984	co	43.500	9.000	13	2.496
Yamauchi 2006	edo	40.900	3.820	6	1.560
Hashimoto 2008	edo	33.500	5.500	21	1.200
Rachmiel 2006	edo	36.270	2.370	18	0.559
Gursoy 2010	edo	36.000	6.200	13	1.720
Figueroa 2004	edo	41.400	5.500	17	1.334
Gateno 2005	ido	42.300	10.460	3	6.039
Rachmiel 2005	ido	34.580	1.980	12	0.572
Gulsen 2007	ido	41.750	6.760	4	3.380

SN-MP Follow-up

Study name	Subgroup within study	Mean	Standard deviation	Sample size	Standard error
Heliovaara 2002 P	co	36.100	3.700	14	0.989
Heliovaara 2002 B	co	40.700	5.800	11	1.749
Heliovaara 2001	co	37.500	6.400	40	1.012
Ward-Booth 1984	co	42.000	8.000	13	2.219
Yamauchi 2006	edo	39.800	3.500	6	1.429
Hashimoto 2008	edo	33.600	5.700	21	1.244
Rachmiel 2006	edo	35.750	2.340	18	0.552
Gursoy 2010	edo	33.700	7.300	13	2.025
Figueroa 2004	edo	40.900	5.000	17	1.213
Gateno 2005	ido	40.350	12.660	2	8.952
Rachmiel 2005	ido	34.430	1.980	12	0.572
Gulsen 2007	ido	39.250	8.070	4	4.035

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