THE IMPACT OF PRESURGICAL ORTHOPEDICS APPLIANCES (PSOAs) IN BILATERAL CLEFT PATIENTS

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF SURGERY (PLASTIC AND RECONSTRUCTIVE SURGERY)

HOSPITAL UNIVERSITI SAINS MALAYSIA
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Acknowledgement

Bismillahirrahmannirrahim

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- My supervisor, Assoc. Prof (Dr.) Wan Azman Wan Sulaiman who continuously spare me his time for consultation, personal guidance, encouragement and advises on various matters throughout this project.
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Impak Kaedah Prasurgeri Ortopedik di Kalangan Pesakit Sumbing

Abstrak

Pengenalan: Pertumbuhan wajah yang baik di kalangan pesakit sumbing dua belah (BCLP) adalah sukar untuk dicapai. Penggunaan prasurgeri ortopedik (PSOA) bertujuan mengurangkan jarak sumbing dengan mambantu pertumbuhan dan pemulihan fungsi. Objektif kajian ini adalah untuk menilai impak prasurgeri ortopedik (PSOA) kepada pertumbuhan wajah di kalangan pesakit BCLP.

Metodologi: Subjek kajian adalah pesakit- pesakit BCLP yang dirawat di Hospital Universiti Sains Malaysia dan Hospital Raja Perempuan Zainab II. Peringkat umur pesakit adalah antara 7 - 21 tahun dengan sumbing tak sindromik dan tiada anomali berkaitan. 'Lateral cephalogram' telah diambil dan dianalisis daripadanya.

Keputusan Kajian: Sampel kajian terdiri daripada 52 pesakit BCLP (26 mempunyai PSOA dan 26 tanpa PSOA). Antara pesakit-pesakit ini, mereka yang mempunyai PSOA mempunyai PNS-ANS (3.69 mm; P = 0.04) dan Co-A (8.38mm; P = 0.04) berbanding dengan mereka yang tidak mempunyai PSOA.

Kesimpulan: Penggunaan prasurgeri ortopedik (PSOA) telah memberikan maksila yang lebih pendek dalam pertumbuhan wajah pesakit sumbing.

Kata kunci: Prasurgeri ortopedik (PSOA), Sumbing dua belah (BCLP)

The Impact of Presurgical Orthopedics Appliances in Cleft Patients

Abstract

Introduction: Acceptable maxillary growth in bilateral cleft lip and palate (BCLP) is difficult to achieve. Presurgical orthopaedic treatment aims at reduction of cleft size by guiding growth and functional rehabilitation. The objectives of this study were to evaluate the impact of Presurgical Orthopaedic Appliances (PSOA) on facial growth in BCLP.

Methods: Subjects were patients who were treated in Hospital Universiti Sains, Malaysia, and Hospital Raja Perempuan Zainab II. Ages ranged 7 – 21 years of age with nonsyndromic cleft and no associated anomalies. A lateral cephalogram was taken and analyzed from it.

Results: The study sample comprised of 52 BCLP patients (26 had PSOA and 26 did not have PSOA). Among these patients, those who had PSOA had PNS-ANS (3.69 mm; P = 0.04) and Co-A (8.38; P=0.04) compared to those who did not have PSOA.

Conclusion: The usage of PSOA gives a shorter maxillary length in the facial growth of bilateral cleft patients.

Keywords: Presurgical Orthopedic Appliance (PSOA), Bilateral Cleft Lip and Palate (BCLP)

1 Introduction

1.1 Background

Cleft lip and palate (CLP) is one of the major health problems worldwide (Goodacre and Swan, 2008). It is a common congenital structural anomaly caused by complex genetic and environmental factors (Cohen and Wexler, 1997). CLP may involve the lip, the roof of the mouth (hard palate), or the soft tissue in the back of the mouth (soft palate). CLP also involves structures around the oral cavity and can extend onto the facial structures resulting in oral, facial, and craniofacial deformity (Boutros and Cutting, 2006; Goodacre and Swan, 2008; Akarsu-Guven *et al.*, 2015). A cleft lip/palate may have a negative impact on an individual's self-esteem, social skills, and behaviour especially among girls (Shah *et al.*, 2016b). Generally, boys are affected more than girls with a ratio of about 3: 2 (Sharma *et al.*, 2012; Akarsu-Guven *et al.*, 2015; Shah *et al.*, 2016b). Males are more likely than females to have a cleft lip with or without cleft palate, while females are at a slightly greater risk for cleft palate alone (Shah *et al.*, 2016b).

1.2 Facial development

According to Abramovich, in 1997 (Yudovich Burak *et al.*, 2014), the facial processes are derived from the neural crest cells of the cranial and vagal area. These will generate the ectomesenquima of the skull-cervical-facial region and the pharyngeal arches. Cell migration and the multiplication result in the formation of the facial process. The branchial oropharyngeal arches arise in the fourth and fifth week of intrauterine development. Initially, there are constituted by mesenchymal tissue, separated by

grooves called pharyngeal clefts. The pharyngeal arches contribute not only to neck formation but also play an important role in face development, mainly the first and second arch. The face is formed between the fourth and eighth week of the embryonic period through the development of the facial processes. There is the cephalicor frontonasal process constitutes the upper edge of the stomodeum or primitive mouth; the maxillary processes that can be seen lateral to the stomodeum, and in a caudal position from the latter, the mandibular processes. In the sixth and seventh week of intrauterine life, the maxillary processes grow simultaneously in a medial direction, compressing the nasal processes toward the midline. In a later stage, the cleft located between the internal nasal process and the maxillary processes covered and they both merge. Consequently, the upper lip is formed by the internal nasal and the maxillary processes (Paradas-Lara *et al.*, 2014).

The craniofacial morphology of subjects with CLP differs from the subjects without any clefts. The lip, nose and maxillary arch of the new-born are frequently severely distorted and asymmetric (Cohen and Wexler, 1997; Kummer, 2000; Bartzela *et al.*, 2011). In babies with unilateral cleft lip and palate (UCLP), the asymmetric nostrils deviated septum, and distorted maxillary arch form gives the biggest challenge in the reconstruction (7). Furthermore, as the bilateral cleft lip and palate (BCLP), the deficient columella and ectopic premaxilla are the primary reconstructive challenges (Graber, 1949; Hart *et al.*, 2000; Doğan *et al.*, 2006). In BCLP, the excessive forward thrusting in the development of the isolated premaxilla is as a result of influences of the vomer and septum (Hayward, 1983). During the 1970s, Latham and others recognized this growth potential and pointed out a possible septal-premaxillary ligament influencing the amount of anterior and upward rotation of the prolabium and premaxilla

(Akarsu-Guven *et al.*, 2015). The width of the maxillary skeleton has reached approximately 80% of its adult size by 4 years of age (Attygalla, 2009). The source of blood supply to the premaxilla is limited to the vomer and septal midline sources, decreasing the circulatory perfusion normally supplemented by anastomosis with the lateral vasculature. This causes some concern about possible interference with blood supply and growth potentials resulting from surgical setback procedures. Early setback may bring bony atrophy and disturb dental development. To avoid malunion, the insertion of a Kirschner wire through the premaxilla and into the vomer has been used. Throughout the 1960s early bone grafts to the premaxillary cleft region at the time of lip repair in infancy were advocated (Attygalla, 2009; Ysunza *et al.*, 2010; Kobayashi *et al.*, 2015). Previously, amputation of the premaxilla is done to facilitate lip closure and avoid the great tension in the repair of the lateral lip components. Severe disturbances of development and gross facial abnormalities are induced when this amputation is carried out at an early age. These reconstructive challenges prompted a better solution for salvage of the premaxilla by innovation of PSOA.

1.3 Epidemiology

Orofacial clefts are one of the most common human congenital disorder reported in Western countries and second most common birth defects among newborn (Yudovich Burak *et al.*, 2015). It is the fourth most common defect and the most common presenting congenital condition of the face (Cohen and Wexler, 1997). The overall incidence of orofacial clefting is approximately one in 700 live births, amounting to approximately 1000 new cases per annum in the UK (Goodacre and Swan, 2008). However, the incidence varies with ethnicity, geographic origin, racial, socioeconomic status and the nature of the cleft itself. In terms of racial group and socioeconomic status, the incidence in whites is 1 in 1,000 births and 1 in 500 in Asians. In Malaysia, the rate of occurrence of cleft was 1.24 per 1000 live births or 1.20 per 1000 deliveries while the latest reported the incidence of 1 in every 700 new born babies had a cleft lip and/or palate condition (Shah *et al.*, 2016a). It was also repo rted that the highest incidence of clefts was among Chinese with 1.9 per 1000 deliveries while the Malays had the lowest incidence with 0.98 per 1000 deliveries (Shah *et al.*, 2016a).

1.4 Aetiology

The aetiology of CLP is complex, including multiple genetic and environmental factors (Liau *et al.*, 2012; Akarsu-Guven *et al.*, 2015; Shaye *et al.*, 2015). Oral clefts frequently occur in combination with a wide range of chromosomal abnormalities and syndromes. Environmental factors include medication during pregnancy, maternal alcohol consumption and smoking, dietary and vitamin deficiencies, diabetes, environmental toxins, altitude, birth order, socioeconomic status, and parental age (Babu Gurramkonda *et al.*, 2016). Approximately 70% of oral clefts are non-syndromic, and only 30% have a syndromic form of cleft (Salahshourifar *et al.*, 2012). In addition, multiple studies have shown strong evidence for the contribution of IRF6 variants to the risk of non-syndromic oral clefts across various ethnic groups (Salahshourifar *et al.*, 2012). Drugs play a limited role in the aetiology of cleft lip or palate CLP; amoxicillin, phenytoin, and thiethylperazine may have some association with CLP. Maternal intake of vasoactive drugs eg. pseudoephedrine, aspirin, ibuprofen, and amphetamine, as well as cigarette smoking, has been associated with higher risk of oral clefts (Kelly and Bardach, 2012). Other drugs such as acne medications containing Accutane and methotrexate, a drug commonly used for treating cancer, arthritis, and psoriasis, may also cause cleft lip and cleft palate (Jones *et al.*, 2011).

1.5 Pre Surgical Orthopedics

Pre Surgical Orthopedics Appliances (PSOAs) is a general term used to describe the treatment of an infant's cleft deformity by repositioning the cleft maxillary segments and the premaxilla prior to the lip and palate reconstruction (Winters and Hurwitz, 1995; Kiya *et al.*, 2015). Its main objective is to reduce the cleft width, re-establish an adequate anatomical relationship and decrease tension between maxillary segments. It is recommended for children with 10 or more mm clefts.

There are different types of infant orthopedics appliances have been described. Active appliances are designed with springs or screws to move the maxillary segments in the desired direction whereas passive appliances induce arch alignment during growth by grinding away material of the plate (Kuijpers-Jagtman and Prahl, 1996; Grayson and Cutting, 2001; Bongaarts *et al.*, 2008; Bongaarts *et al.*, 2009a; Bongaarts *et al.*, 2009b). Nasoalveolar moulding is also part of the treatment protocol. It is believed to help in reduction of soft-tissue and cartilaginous deformity. This is to facilitate surgical soft-tissue repair in optimal conditions under minimal tension to minimize scar formation (Catharina A. M. Bongaarts *et al.*, 2008; Bartzela *et al.*, 2011).

The usage of dental devices to assist in CLP management goes way back to the 16th century, describing the retraction of a protruded premaxilla in BCLP (Winters and Hurwitz, 1995; Barry H. Grayson and Court B. Cutting, 2001; Bongaarts *et al.*, 2009b; Kiya *et al.*, 2015). Mc Neil in 1950s, introduced the concept dentofacial orthopaedics to align the maxillary segments in unilateral CLP and to bring the pre maxilla towards

the midline in bilateral CLP (Bongaarts *et al.*, 2008; Catharina A. M. Bongaarts *et al.*, 2008; Bongaarts *et al.*, 2009b). On the other hand, Millard and Latham advocated that repositioning of the maxillary segments preoperatively, provided a more symmetric, enhanced the closure of the alveolar clefts and reduce the width of the alveolar cleft (Kuijpers-Jagtman and Prahl, 1996; Barry H. Grayson and Court B. Cutting, 2001; Kiya *et al.*, 2015). Ortiz Monasterio in 1966 demonstrated in his study that CLP adult patients who were not surgically treated, did not exhibit midface growth restriction(Xu *et al.*, 2014).

Friede and Pruzansky in 1972 (Farronato *et al.*, 2014), were not in favour of orthopedic-surgical treatment. They claimed that there was growth restriction that caused concave profiles due to maxillary retrusion and believed that it was best to re-establish the continuity of labial musculature early after birth to allow natural muscular forces that mould the palate to normalize the distorted oral and pharyngeal skeletal architecture.

Passive intraoral appliances are meant to guide skeletal growth in the desired direction or even stimulate growth. However, in certain cases, passive appliances cannot provide the ideal result, particularly in patients with protruding premaxilla. In such patients, active intraoral appliances can direct premaxillary growth in the downward and backward direction by the application of force to the premaxilla, with highly predictable outcomes(Kiya et al., 2015). In 2004 Berkowitz (Cruz, 2016) described the long-term consequences of the Latham's orthopaedic device which would not produce a harmonious development of the face and palate. However in 2004 Pérez19et al (Yudovich Burak *et al.*, 2014) reported favourable results with the use of Latham's

device in 14 patients through photographic and cephalometric records of 11 mm expansion of the maxillary process and 18 mm retrusion in the transverse dimension. Improvements in orthodontic and surgical techniques have allowed cleft surgery to be performed at an ever earlier age. Even a technically excellent operation does not avoid the well-known growth-inhibiting impact of surgery. Such impact becomes apparent in many anomalies with transversal, sagittal and vertical growth inhibition of deciduous teeth. To expect a long term evidence of the efficiency of orthopaedic therapy in infants is illusory in those cases. A prerequisite for guiding and directing dental growth by orthodontic means is to avoid any radical growth-inhibiting measure during cleft surgery. Only then presurgical orthopaedic treatment will have a long lasting success.

1.6 Cephalometric studies

Cephalometric studies can be defined as a scientific study of the measurements of the head with relation to specific reference points that has been used for evaluation of facial growth and development, including soft tissue profile (Bongaarts *et al.*, 2009a). It is an accepted method to assess anomalies in the craniofacial skeleton and provides an objective documentation of postoperative results. Despite the number of proposed cephalometric evaluations, no single method has been demonstrated to be superior (Bongaarts *et al.*, 2009b). Thus, this study allows us to compare these patients, so that differences between the patient's actual dentofacial relationships and those expected for his/her racial or ethnic groups are revealed

1.7 Aims of research study

Cleft lip and palate (CLP) affects craniofacial growth, especially in the midface area, resulting in functional, aesthetic as well as psychosocial disturbance (Yudovich Burak *et al.*, 2015; Shah *et al.*, 2016b) Apart from intrinsic growth deficiency, facial growth in cleft lip and palate may be affected due to surgical interventions, creating lip tension and scar tissue surrounding the palate and maxilla (Tan *et al.*, 2015). Presurgical orthodontic treatment can also cause adverse effects in facial growth (Tan *et al.*, 2015; Colbert and Van Eeden, 2017). Intrinsic tissue deficiency has been identified as a factor for the maxillary hypoplasia observed in the group of CLP patients with median facial dysplasia. These patients have obvious tissue deficiency even before any surgical repair, as characterized by hypoplasia of the nose, prolabium, premaxilla and palate.The timing of cleft palate repair is the most significant factor (Lee and Liao, 2013). There are many controversies in the literature about the optimal timing of palate repair. Some studies have reported that delayed palate repair may lead to better craniofacial morphology (Xu *et al.*, 2012).

The main objective of cleft lip/palate treatment is to optimize maxillofacial growth, speech development, hearing and to achieve good aesthetic outcomes. Cleft palate repair has a more deleterious effect on craniofacial growth than cleft lip and alveolus repair (Akarsu-Guven *et al.*, 2015).Currently, no general consensus has been reached concerning the optimal timing of cleft repair. It is however generally accepted (Farronato *et al.*, 2014) that palatal surgery is one of the main factors impeding mid-facial growth in patients with orofacial clefts (Farronato *et al.*, 2014). Initially, cleft

palate surgery focused on the immediate surgical closure of the cleft, often causing extensive dental distortions with long-term mid-face hypoplasia (Xu *et al.*, 2012). A trend of delaying palatal repair followed in order to diminish the amount of maxillary growth restriction (Ysunza *et al.*, 2010). Delaying palate repair, however, impedes adequate speech development. The maxillary growth is reflected in vertical, anterior-posterior and transverse dental arch relationships, making arch relationships one of the main outcomes after cleft repair.

A randomized clinical trial in the Netherlands Kuijpers- Jagtman and Prahl (Kuijpers-Jagtman and Prahl, 1996) has shown that the traditional PSOA has not been able to help with the feeding, improvement of speech or minimization of treatment at a later age. However, the PSOA nasoalveolar molding has surpassed the traditional goals in improving long term- nasal esthetics, reducing the number of nasal surgical procedures, no worsening of growth is found for patients undergoing primary reconstructive surgery and ultimately saving costs to the patients and society by reducing the number of surgical hospital admissions (Chaudhary *et al.*, 2016). Unfortunately, all these studies are done in the Western countries and all the cephalometric values are based on the Caucasian population. The baseline values for this study would be promising to show how the impact of PSOA on facial growth to our local cleft population.

1.8 General objective

To evaluate the impact of PSOA on facial growth in BCLP patients.

1.9 Specific objectives

a) To determine the facial growth of BCLP with PSOA.

b) To determine the facial growth of BCLP without PSOA.

c) To compare the facial growth of BCLP with and without PSOA.

2 Study Protocol

2.1 Documents Submitted for Ethical Approval

Several documents have been submitted for ethical approval including patient's informed consent and data collection sheet (Appendix E1). Written informed consent was obtained from all subjects or family`s representative either parent or guardian. They were divided into 4 age categories consisting of 7-11 years old (Appendix A1-A8), 12-14 years old (Appendix B1-B8), 15-17 years old (Appendix C1-C9), and 18-21 years old (Appendix D1 –D8).

2.1.1 Ethical Approval Letter

This research project was approved by the Research Ethics Committee (Human) of the Universiti Sains Malaysia (USM) Health Campus, Kubang Kerian and Medical Research Ethics Committee from National Medical Research Register (NMRR), Ministry of Health, Malaysia. Approval letters were as follows:

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

Ruj.Kami :(13)KKM/NIHSEC/ P17-599
Tarikh : **05-Jun-2017**

DR SALIZA BINTI AINUDIN YEAP
HOSPITAL UNIVERSITI SAINS MALAYSIA

Dato'/ Dr/ Tuan/ Puan,

SURAT KELULUSAN ETIKA:

NMRR-17-461-33882 (IIR)
NO. PROTOKOL : N/A
IMPACT OF PRESURGICAL ORTHOPEDICS IN CLEFT PATIENTS

Dengan hormatnya perkara di atas adalah dirujuk.

2. Bersama dengan surat ini dilampirkan surat kelulusan saintifik dan etika bagi projek ini. Segala rekod dan data subjek adalah *SULIT* dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah Hospital / Institusi di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Dato'/ Tuan/ Puan perlu akur dan mematuhi keputusan tersebut.

3. Penyelidik- penyelidik yang terlibat ialah:

   Hospital Raja Perempuan Zainab II
   Dr Saliza Binti Ainudin Yeap (Penyelidik Utama)

   Universiti Sains Malaysia Hospital
   Dr Saliza Binti Ainudin Yeap (Penyelidik Utama)

4. *Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga* **04-Jun-2018**. Tuan/Puan perlu menghantar dokumen-dokumen seperti berikut selepas mendapat kelulusan etika. Borang-borang berkaitan boleh dimuat turun daripada laman web Jawatakuasa Etika & Penyelidikan Perubatan (JEPP) (http://www.nih.gov.my/mrec).

   i. ***Continuing Review Form*** selewat-lewatnya dalam tempoh 1 bulan (30 hari) sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
   ii. ***Study Final Report*** pada penghujung kajian.
   iii. Mendapat kelulusan etika sekiranya terdapat pindaan ke atas sebarang dokumen kajian/ lokasi kajian/ penyelidik.
   iv. Kajian berkenaan intervensi klinikal sahaja: Laporan mengenai ***all Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs)*** dan ***Protocol Deviation/Violation*** di lokasi kajian yang diluluskan oleh JEPP jika berkenaan. *SAE* perlu dilaporkan dalam tempoh 15 hari kalender dari kesedaran kejadian (*awareness of event)* oleh penyelidik. Laporan awal *SUSAR* perlu dikemukakan seawal mungkin tapi tidak melewati 7 hari calendar dari kesedaran kejadian oleh penyelidik, disusuli dengan laporan lengkap dalam tempoh tambahan 8 hari kalender.

5. Bilangan subjek/ pesakit/ responden yang disasarkan untuk menyertai kajian ini di Malaysia adalah **98 orang**.

6. *Sila ambil maklum* bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

.....

DATO' DR CHANG KIAN MENG
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

s.k:

HRRC HOSPITAL RAJA PEREMPUAN ZAINAB II

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

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29th March 2017

019-9166761

Dr. Saliza Ainudin Yeap
Reconstructive Sciences Unit
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/17010004
Protocol Title : Impact of Presurgical Orthopedics Appliances (PSOAs) in Cleft Patients.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/17010004**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **29th March 2017** until **28th March 2018.**

Study Site: Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II (HRPZ II), Kota Bharu, Kelantan.

The following researchers also involve in this study:

1. Assoc. Prof. Dr. Wan Azman Wan Sulaiman
2. Dr. Ahmad Burhanuddin Abdullah
3. Dr. Wan Ratmaazila Wan Makhtar
4. Miss Fareha Aleas

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Parental Information Sheet and Consent Form – English version
2. Parental Information Sheet and Consent Form – Malay version
3. Patient Information Sheet and Assent Form – English version – 12-14 Years Old
4. Patient Information Sheet and Assent Form – Malay version – 12-14 Years Old
5. Patient Information Sheet and Assent Form – English version – 15-17 Years Old
6. Patient Information Sheet and Assent Form – Malay version – 15-17 Years Old
7. Patient Information Sheet and Consent Form – English version – 18-21 Years Old
8. Patient Information Sheet and Consent Form – Malay version – 18-21 Years Old
9. Data Collection Sheet – English version
10. Data Collection Sheet – Malay version

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2015: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.

2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2015: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2015: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2014: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2015.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2014: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,

PROF. DR. HANS AMIN VAN ROSTENBERGHE
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

2.1.2 Study Protocol

A study protocol which had been submitted after considering all the amendments by research committee is attached as follows:

SCHOOL OF MEDICAL SCIENCES
UNIVERSITI SAINS MALAYSIA

SHORT TERM GRANT RESEARCH PROPOSAL

TITLE:
THE IMPACT OF PRESURGICAL ORTHOPEDICS APPLIANCES (PSOAs) IN BILATERAL CLEFT PATIENTS

Prepared by:

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Cik Fareha Aleas (PI)
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1. LITERATURE REVIEW

Cleft lip and palate (CLP) is one of the major health problems worldwide [1]. It is the fourth most common defect and the most common presenting congenital condition of the face [2]. The overall incidence of orofacial clefting is approximately one in 700 live births, amounting to approximately 1000 new cases per annum in the UK [1]. However, the incidence varies with ethnicity, geography and the nature of the cleft itself. In terms of racial group and socioeconomic status, the incidence in whites is 1 in 1,000 births and 1 in 500 in Asians. In Malaysia CLP affected 1: 941 births [3].

The craniofacial morphology of subjects with CLP differs from the subjects without any clefts. The lip, nose, and maxillary arch of the new-born are frequently severely distorted and asymmetric [2, 4, 5]. In babies with unilateral cleft lip and palate (UCLP), the asymmetric nostrils, deviated septum, and distorted maxillary arch form gives the biggest challenge in reconstruction (6-8). Furthermore, as the bilateral cleft lip and palate (BCLP), the deficient columella and ectopic premaxilla are the primary reconstructive challenges [6-8].

Pre Surgical Orthopedics Appliances (PSOAs) is a general term used to describe treatment of an infant's cleft deformity before the definitive reconstructive surgery [9, 10] .The usage of dental devices to assist in CLP management goes way back to the 16^{th} century, describing the retraction of a protruded premaxilla in BCLP [9-12]. Mc Neil in 1950s, introduced the concept orthopedics treatment for infants with complete cleft lip/palate before primary surgical repair [12-14]. On the other hand, Millard and Latham advocated that repositioning of the maxillary segments preoperatively, provided a more symmetric, enhanced the closure of the alveolar clefts and reduce the width of the alveolar cleft [9, 11, 15].

There are different types of infant orthopedics appliances have been described. Active appliances are designed with springs or screws to move the maxillary segments in the desired direction whereas passive appliances induce arch alignment during growth by grinding away material of the plate [12, 13, 15-17]. Nasoalveolar moulding is also part of the treatment protocol. It is believed to help in reduction of soft-tissue and cartilaginous deformity. This is to facilitate surgical soft-tissue repair in optimal conditions under minimal tension to minimize scar formation [4, 14].

Cephalometric studies can be defined as a scientific study of the measurements of the head with relation to specific reference points that has been used for evaluation of facial growth and development, including soft tissue profile [7, 18, 19]. It is an accepted method to assess anomalies in the craniofacial skeleton and provides an objective documentation of postoperative results. Despite the number of proposed cephalometric evaluations, no single method has been demonstrated to be superior [7]. Thus, this study allows us to compare the patient with a normal reference group, so that differences between the patient's actual dentofacial relationships and those expected for his/her racial or ethnic groups are revealed

A randomized clinical trial in the Netherlands Kuijpers- Jagtman and Prahl [15] has shown that the traditional PSOA has not been able to help with the feeding, improvement of speech or minimization of treatment at a later age. However, the PSOA nasoalveolar molding has surpass the traditional goals in improving long term- nasal esthetics, reducing the number of nasal surgical procedures, no worsening of growth is found for patients undergoing primary reconstructive surgery and ultimately saving costs to the patients and society by reducing the number of surgical hospital admissions [11].

Unfortunately, all these studies are done in the Western countries and all the cephalometric values are based on the Caucasian population. The baseline values for this study would be promising to show how the impact of PSOA on facial growth to our local cleft population.

2. OBJECTIVES

2.1. General objective

a) To determine the impact of PSOA on facial growth in BCLP patients

2.2. Specific objectives

a) To determine the facial growth of BCLP patients with PSOA
b) To determine the facial growth of BCLP patients without PSOA
c) To compare the facial growth of BCLP patients with and without PSOA

3. HYPOTHESIS

3.1. Null hypothesis*:* There is no significant impact of PSOA on facial growth in cleft patients

3.2. Alternative hypothesis*:* There is a significant impact of PSOA on facial growth in cleft patients

4. METHODOLOGY

4.1 Study design

This is a prospective cohort study of 52 subjects with orofacial clefts aged 7 to 21 years old treated at Plastic and Reconstructive Surgery Department, Hospital Universiti Sains Malaysia (HUSM), 16150 Kubang Kerian, Kelantan and Orthodontic Department, Hospital Sultanah Raja Perempuan Zainab II (HRPZ ll), 15586 Kota Bharu, Kelantan.

4.2 Study population

4.2.1 Reference population

All treated cleft patients in Kelantan from January 1997 to December 2015

4.2.2. Source population

All treated cleft patient patients from Department of Plastic and Reconstructive Surgery in HUSM, Kelantan and Orthodontic Department in Hospital Sultanah Raja Perempuan Zainad II, Kelantan from January 1997 to December 2015

4.2.3. Sampling frame

The patients that fulfill the criteria of inclusion and exclusion criteria will be selected

4.3. Study duration

1 June 2016 – 30 June 2017

4.4 Study location

1. Department of Plastic & Reconstructive Surgery, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan

2. Orthodontic Department in Hospital Sultanah Raja Perempuan Zainab II, Kelantan

4.5. Sampling method

Convenient sampling of treated cleft patients from the above department will be done.

4.6 Subjects

All subjects will be recruited from previous medical records. Written assent and informed consent will be obtained from all potential subjects who met the inclusion criteria (as listed in section 4.7) before participating in this study. Subjects will be divided according to respective groups based on their diagnosis. All data collected will be documented in the data collection sheet. Patients will be subjected to undergo a lateral cephalogram imaging.

4.7 Inclusion and exclusion criteria

Inclusion Criteria	**Exclusion criteria**
• All cleft patients • 7-21 years of age • Good quality, well-oriented, lateral cephalometric radio- graphs were available for each patients • No orthognathic or facial cosmetic surgery had been previously performed	• Defaulter • Untraceable medical records • Syndromic patients • Vitamin Deficiency disorder

4.8 Sample size calculation

Sample size were calculated for each specific objectives. The sample size for Objective 1 and 2 were calculated by single mean formula as follow:

$$n = \left(\frac{z\sigma}{\Delta}\right)^2$$

The parameters used were defined as:

α: Significance level

β: Power

σ: Standard deviation reported from previous study

δ : Detectable difference by expert opinion

Table 2.1 Sample size calculation using single mean formula

Objectives	$\boldsymbol{\alpha}$	$\boldsymbol{\beta}$	$\boldsymbol{\sigma}$	$\boldsymbol{\delta}$	**n**	**Total sample size (including 10% drop out)**
Objective 1 [18]	0.05	0.80	0.15	0.05	35	40
Objective 2 [18]	0.05	0.80	0.20	0.05	61	68

The sample size for Objective 3 and 4 were calculated by two means formula as follow. Power and sample size (PS) Software was used to calculate the estimated sample size.

$$n = \frac{2\sigma^2}{\delta^2}\left(z_\alpha + z_\beta\right)^2$$

The parameters used were defined as:

α: Significance level

β: Power

σ: Standard deviation of either group

δ: Estimated mean difference between groups

m: ratio of 1:1

Table 2.2 Sample Size Calculation Using Two Means Formula

Objectives	$\boldsymbol{\alpha}$	$\boldsymbol{\beta}$	$\boldsymbol{\sigma}$	$\boldsymbol{\delta}$	**n**	**Total sample size (including 10% drop out)**
Objective 3 [19]	0.05	0.80	1.24	1	25 x 2 = 50	56
Objective 4 [19]	0.05	0.80	0.97	1	16 x 2 = 32	36

The selected sample size for this study including 10% drop-out rate was 68 patients.

4.9 Cephalometric analysis

All selected subjects will be invited to our clinic at the Plastic and Reconstructive Surgery Department, Hospital Universiti Sains Malaysia (HUSM), 16150 Kubang Kerian, Kelantan. The lateral cephalogram will be taken at the clinic. Procedure will take around 15 minutues. Anthropometric measurement will be performed precisely by using the Dental Imaging Software System 6.14.7. All data will be analyzed by statistical analysis using SPSS software.