Review Article

Protocols in Cleft Lip and Palate Treatment: Systematic Review

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Objectives. To find clinical decisions on cleft treatment based on randomized controlled trials (RCTs). Method. Searches were made in PubMed, Embase, and Cochrane Library on cleft lip and/or palate. From the 170 articles found in the searches, 28 were considered adequate to guide clinical practice. Results. A scarce number of RCTs were found approaching cleft treatment. The experimental clinical approaches analyzed in the 28 articles were infant orthopedics, rectal acetaminophen, palatal block with bupivacaine, infraorbital nerve block with bupivacaine, osteogenesis distraction, intravenous dexamethasone sodium phosphate, and alveoloplasty with bone morphogenetic protein-2 (BMP-2). Conclusions. Few randomized controlled trials were found approaching cleft treatment, and fewer related to surgical repair of this deformity. So there is a need for more multicenter collaborations, mainly on surgical area, to reduce the variety of treatment modalities and to ensure that the cleft patient receives an evidence-based clinical practice.

1. Introduction

Orofacial clefts are the most prevalent craniofacial birth defects and the second most common birth anomaly, second only to clubfoot [1]. In the United States of America, it is estimated that $100,000 are spent to rehabilitate a child born with oral cleft [2].

The approach of the patient with cleft lip and palate is multidisciplinary, and the cleft team should be ideally composed by craniofacial surgeons, otolaryngologists, geneticists, anesthesiologists, speech-language pathologists, nutritionists, orthodontists, prostodontists, and psychologists, and to be capable of treating even rare facial clefts with excellence, neurosurgeons, and ophthalmologists. In this manner, it is possible to provide long-term followup through the entire child’s development and achieve all of the following treatment goals: normalized facial aesthetic, integrity of the primary and secondary palate, normal speech and hearing, airway patency, class I occlusion with normal masticatory function, good dental and periodontal health, and normal psychosocial development [3].

The most broadcast treatment modalities in the management of unilateral cleft lip and palate are listed in Table 1 (chronologic age) and Table 2 (dentofacial development).

The presented management of cleft lip and palate is not accepted exactly by all cleft centers, and there is a striking diversity of clinical practice in the area [4]. Evidence-based medicine should be the answer to the uncertainties in the treatment; however there is a paucity of high level of evidence (i.d. systematic reviews and randomized controlled trials [5]) on cleft lip and palate [6]. Therefore, many clinical decisions are made based on biased evidence, such as the decision of when to perform secondary bone graft, which is answered by many surgeons with the information of a retrospective study [7].

Aiming to find clinical decisions based on randomized controlled trials (RCTs), searches on cleft lip and/or palate were done in three main scientific databases: Cochrane Library, Embase, and PubMed [8]. Posteriorly, we selected articles that could validate or change the presented management.
Table 1: Treatment modalities in the management of unilateral cleft lip and palate which are often based on chronologic age.

| Timing                        | Procedure                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| After 16 weeks of pregnancy   | Cleft lip diagnosis by ultrasound images (palate is more difficult to acquire) [9] |
|                               | Discussion with a craniofacial surgeon [10]                                |
| Prenatal                      | Consultation with a geneticist/dysmorphologist [10]                        |
|                               | If the child has cleft palate, specialized nipples and bottles are necessary to improve feeding after birth [11] |
| Neonatal                      |                                                                           |
| 12 weeks of age               | Cleft lip repair [12]                                                      |
| 6–12 months of age            | Cleft palate one-stage repair with intravelar veloplasty [13]             |
| 5 years                       | Secondary rhinoplasty [14]                                                 |

Table 2: Treatment modalities in the management of unilateral cleft lip and palate which are often based on dentofacial development.

| Timing                        | Procedure                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| Prior to cleft lip repair     | Presurgical infant orthopedics [15]                                       |
| Primary dentition             | Orthodontic treatment for maxillary expansion [16]                         |
| Mixed dentition               | Orthodontic treatment for maxillary expansion and maxillary protraction [16] |
| Before eruption of permanent dentition | Secondary alveolar bone graft with cancellous bone from iliac crest [10, 17] |
| Permanent dentition           | Orthodontic treatment for dental arches alignment [18]                    |
| After fully eruption of permanent dentition, dental arches alignment, and end of the maxillofacial growth | Orthognathic surgery for maxillary advancement [16] |
| After orthognathic surgery    | Postsurgical orthodontics for closure of residual spaces and occlusion final adjustments [19] |
|                               | Replacement of missing teeth by a prosthodontist [20]                     |

The main descriptors used were as follows:

(i) MeSH: “cleft lip,” “cleft palate”;
(ii) Emtree: “cleft lip palate,” “cleft lip,” “cleft palate.”

2.1. Cochrane Library. The searches in this database were made in “Search History,” and the search strategy was assembled in “Search For.”

We used MeSH descriptors when available, and free-text truncated with an asterisk. The following expression was added to the search strategy: “AND (randomized controlled trial∗):ti,ab,kw.” Only the results in “Cochrane Central Register of Controlled Trials” were considered.

2.2. Embase. The searches in this database were made in “Advanced Search,” selecting the following items: “Map to preferred terminology (with spell check),” “Also search as free text,” and “Include sub-terms/derivatives.” In “Records from,” we selected only “Embase.”

We used Emtree descriptors and selected the item “Randomized Controlled Trial” in “Advanced Limits,” option “Evidence Based Medicine.”

2.3. PubMed. The searches in this database were made in “Search details.”

We used MeSH descriptors when available, and free-text truncated with an asterisk. Additionally, we selected “Randomized Controlled Trial” in “Limits,” option “Type of Article.”

All abstracts provided by the databases in the searches were collected, resulting in a total of 170 different articles. From these abstracts, studies that clearly were not RCTs (e.g., reviews and case series) or not focused on cleft treatment were excluded. As a result, we were left with 88 papers. Posteriorly, we searched “Portal de Periódicos da CAPES” (http://www.capes.gov.br/) for the full-text articles. After meticulous reading of the studies, we verified that 53 of the 88 articles were really RCTs. Next, the approaches compared in each study were analyzed, in order to select articles in which the comparisons discussed appeared in two or more of the 53 studies. At the end of the selection, 28 articles were included for the analysis of the obtained conclusions. One paper on infant orthopedics was excluded since it emphasized a methodological fault on the study design (i.d. sample heterogeneity). The flowchart below (Figure 1) outlines the process of articles selection.

3. Results

The search results were recorded in Figure 2.

The issues discussed by the 28 selected articles were as follows:

(i) infant orthopedics: 15/28 = 53.57%;
(ii) postoperative pain relief: 5/28 = 17.86%;
(iii) management of the cleft maxillary hypoplasia: 4/28 = 14.28%;
(iv) perioperative steroids: 2/28 = 7.14%;
(v) alveoloplasty: 2/28 = 7.14%.

2. Methods

On March 3, 2012, searches for RCTs were made in three databases (Cochrane Library, Embase, and PubMed) on cleft lip and/or palate. When appropriate, we used search strategies involving the MeSH descriptors and Emtree, Boolean logic operators, and free-text truncated with an asterisk.
4. Discussion

RCTs and systematic reviews of these studies are considered the best levels of evidence to conduct clinical practice [49]. For this reason, we searched for RCTs that could orientate the cleft lip and/or palate treatment, which is marked by a great number of approaches [10]. To find the RCTs we used two main databases proposed by World Health Organization (i.e. PubMed and Embase) [8] and the Cochrane Library, reference of studies for evidence-based medicine practice [50]. Therefore, from the 170 articles found in the searches for RCTs, we reached 28 final studies that approached therapeutic practices on cleft patient. The issues of these 28 articles were collected together with their conclusions.

During this study, a scarce number of RCTs were found approaching cleft treatment. This fact is confirmed by the literature, which showed in 2004 that only 6% of RCTs in “Plastic and Reconstructive Surgery,” “British Journal of Plastic Surgery,” and “Annals of Plastic Surgery” approached cleft lip and/or palate [51]. In an article of 2007, it is possible to observe that the lack of studies with high level of evidence is a problem present in the whole plastic surgery, resulting in the following distribution of articles from the 16 leading journals in the area: case report, 80%; RCTs, 2%; and meta-analysis, <1% [52].

In the final sample of 28 articles, we verified the presence of five issues, arranged here in descending order by number of studies that addressed them: infant orthopedics, postoperative pain relief, management of the cleft maxillary hypoplasia, and perioperative steroids and alveoloplasty. The issues of the selected articles are consistent with...
| Table 3: Conclusions of articles that addressed “infant orthopedics”. |
|---------------------------------|-----------------|---------------------------------|
| Experimental group | Conclusion | Control | Explanation for the conclusion |
|---------------------|-------------|---------|---------------------------------|
| Patients who had infant orthopedics | = | Patients who did not have infant orthopedics | Cephalometric outcomes at ages 4 and 6 were not relevant [21]; no long-term (age 6 [22]) or short-term (18 months [23]) outcomes on facial appearance; no influence on mother’s satisfaction [24]; no improvement on feeding efficiency or general body growth within the first year [25, 26]; no long-term outcomes on the maxillary arch dimensions (age 6 [27]), on deciduous dentition (age 6 [27, 28]), or on the occlusion (age 6 [28]); no short-term outcomes on the maxillary arch dimensions (18 months) [29, 30]; no long-term outcomes on the maxillary arch dimensions (age 6) [31]; no improvement on the intelligibility at 2.5 years [32]. |
| Patients who had infant orthopedics | > | Patients who did not have infant orthopedics | Acceptable cost effectiveness based on speech development at 2.5 years [33]; better speech development between 2 and 3 years [34]; higher ratings for intelligibility at 2.5 years [35]. |

| Table 4: Conclusions of articles that addressed “postoperative pain relief”. |
|---------------------------------|-----------------|---------------------------------|
| Experimental group | Conclusion | Control | Explanation for the conclusion |
|---------------------|-------------|---------|---------------------------------|
| Rectal Acetaminophen | > | Rectal placebo | In children who underwent palatoplasty, acetaminophen (40 mg/kg administered in the operating room at the end of surgery, and 30 mg/kg every 8 hours until 48 hours) was more effective in pain control than placebo [36]. |
| Rectal Acetaminophen (40 mg/kg) | = | Rectal placebo | Acetaminophen and placebo were equivalents in regards to nauseas and vomits, the most frequent adverse effects [36]. Rectal acetaminophen (administered at anesthesia induction) did not result in analgesic plasma concentrations and it was not effective in pain control after palatoplasties [37]. |
| Bilateral Palatal Block with Bupivacaine (0.5 mL of 0.25% solution at greater palatine, lesser palatine, and nasopalatine foramina) | = | Plain saline (0.5 mL at each point) | Bupivacaine and saline were effective in the palatal block and provided good parental satisfaction. Both provided better postoperative analgesia than the no block group [38]. |
| Bilateral Infraorbital Nerve Block with Bupivacaine | > | Plain saline | In children who underwent cleft lip repair, the injection of 1.5 mL of 0.25% bupivacaine (extra-oral approach) [39] or 1–1.5 mL of 0.5% bupivacaine (intraoral approach) [40] in the area of infraorbital foramen provided safe and prolonged postoperative pain relief (at least 8 hours [39]). |

*All the alveoloplasties used iliac crest bone graft.*

| Table 5: Conclusions of articles that addressed “management of the cleft maxillary hypoplasia”. |
|---------------------------------|-----------------|---------------------------------|
| Experimental group | Conclusion | Control | Explanation for the conclusion |
|---------------------|-------------|---------|---------------------------------|
| Osteogenesis distraction | = | Le Fort I osteotomy | No significant differences were found in development of velopharyngeal insufficiency postoperatively [41, 42] and patient morbidity (infection and occlusion disturbance) [43]. |
| Osteogenesis distraction | > | Le Fort I osteotomy | Better skeletal stability in maintaining the maxillary advancement in the long term [43, 44]. |
especially with the advent of bone substitutes [60].

studies [46]; alveoloplasty is a highly debated intervention,

A survey of 2003 supports this fact reflects the lack of RCTs on surgical procedures itself.

That explains the difficulty of treating orofacial clefts related to over 300 syndromes [62], and the twenty percent of all clefts have other congenital abnormality, part of a known syndrome or not [63].

From the five issues, only two approached the surgical act, resulting in 21.43% (6/28) of the selected articles. This fact reflects the lack of RCTs on surgical procedures itself. A survey of 2003 supports this affirmation, which estimates that only 3.4% of the publications on the main surgical journals were RCTs [61].

From the final sample, 53.57% were composed by articles approaching infant orthopedics. That was due to the fact that 14 of the 15 studies on this issue were part of the Dutch Intercenter Study (Dutchcleft), a great effort to analyze the effects of presurgical infant orthopedic treatment in complete unilateral cleft lip and palate [32].

No study in the selected sample analyzed specifically a cleft patient with a syndrome or congenital abnormality. That explains the difficulty of treating orofacial clefts related to over 300 syndromes [62], and the twenty percent of all children with a cleft that have other congenital abnormality, part of a known syndrome or not [63].

From the 15 studies approaching infant orthopedics, only 3 found a benefit of this treatment, an improvement of the patient speech at nearly 2.5 years old [33–35]. However, when the language development was evaluated in the long term, at nearly 6 years old, there were no differences between experimental group and control [31]. On the other hand, all of the 14 Dutchcleft studies used only the Zurich approach to treat their patients whereas the other articles applied a passive and an active maxillary orthopedic treatment. So, in our systematic review we did not find RCTs about nasoalveolar molding therapy, a promising practice in presurgical infant orthopedics [54]. Non-RCTs studies have been appointing to the benefits of nasoalveolar molding therapy: long-term aesthetic outcomes [64–66] and better nasal symmetry [67].

Four distinct comparisons were found on postoperative pain relief: rectal acetaminophen versus placebo, bilateral nerve block with bupivacaine versus plain saline, continuous intravenous dextrose sodium phosphate [36], whereas the other one did not observe effective pain control (single prophylactic dose of 40 mg/kg) [37], emphasizing the fact that both analyzed palatoplasties. These results are in concordance with the standard clinical practice that states a postoperative rectal loading dose (30–40 mg/kg) followed by regular maintenance doses (20 mg/kg 6 hourly or 30 mg/kg 8 hourly) [68–70]. Besides the difficulties associated with rectal administration (e.g., delayed and erratic absorption), an RCT done in patients undergoing craniostenosis repair verified a higher efficacy than oral administration [68].

On the comparison of bilateral nerve block with bupivacaine versus plain saline, there were one article approaching palatal block [38] and two approaching infraorbital nerve block [39, 40]. Prabhu et al. proved with a randomized, double blind, prospective clinical trial that bilateral infraorbital nerve block with bupivacaine is more effective than peri-incisional infiltration in postoperative pain relief after cleft lip repair [71], and it became a standard clinical practice in cleft care [72, 73]. However, the scientific literature does not clarify which volume should be used to make this block,
so there is evidence defending 0.5 mL of 0.5% bupivacaine in each side [74], 3 mL of 0.5% bupivacaine [75], and 0.5–1 mL of 0.5% bupivacaine [73]. Since very small doses of bupivacaine have serious side effects, such as cardiac dysrhythmias and neurotoxicity [76], more studies need to be done to standardize this technique. In regards to the article that analyzed palatal block, there were no differences between experimental group (0.5 mL of 0.25% bupivacaine at each point) and control (0.5 mL of plain saline at each point), with both resulting in postoperative analgesia. Besides the extensive use of palatal block [77], including in Smile Train [78], the results of the selected RCT led us to conclude that the analgesic effects are results from the liquid pressure, not from the anesthetic solution. Such results appeared in a similar manner with Van Gheluwe and Walton, explaining the analgesic effect of intrapulpal saline injection with the pressure that it exerts [79].

In regards to the studies that addressed the management of cleft maxillary hypoplasia [41–44] there was only one comparison, distraction osteogenesis versus Le Fort I osteotomy. There were no divergences in the studies conclusions, leading to a possible superiority of distraction osteogenesis over the conventional technique. However, the scientific literature induces us to conclude that the choice between distraction osteogenesis and conventional orthognathic surgery is dependent on advancement length. Baek et al. published a controlled clinical trial comparing these techniques in which they realize this fact [80]. Scolozzi, in a review of 80 scientific articles, concludes that distraction osteogenesis should be done to standardize this technique. In regards to the article that analyzed palatal block, there were no divergences between

5. Conclusion

Few randomized controlled trials were found approaching cleft treatment, and fewer related to surgical repair of this deformity. From the found articles, only a small percentage reported the study with known quality parameters. However, one consistent conclusion could be verified due to fourteen Dutchcleft RCTs; there is no high-level evidence supporting the use of infant orthopedics by Zurich approach. So there is a need for more multicenter collaborations, mainly on surgical area, to reduce the variety of treatment modalities and to ensure that the cleft patient receives an evidence-based clinical practice.

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