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Systematic Review
Cleft Lip and Palate

Grafting materials for alveolar cleft reconstruction: a systematic review and best-evidence synthesis

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Abstract. The purpose of this study was to compare the efficacy of alveolar bone reconstruction for alveolar cleft patients performed with the traditional iliac graft or alternative/supplementary bone grafting materials. Electronic databases, relevant journals, and reference lists of the included studies were searched to the end of June 2016. A best-evidence synthesis was performed to draw conclusions. A total of 38 studies were included, which provided 25 pieces of evidence: seven of moderate evidence and 18 of insufficient evidence. The seven pieces of moderate evidence indicated that (1) bone morphogenetic protein 2 bound to absorbable collagen sponge shares similar cleft repair efficacy to the iliac graft; (2) covering the iliac graft with an acellular dermis matrix membrane may increase bone retention for unilateral cleft patients; (3) mixing iliac graft with platelet-rich plasma may increase bone retention for skeletally mature patients, but (4) does not achieve the same result for younger patients; and compared with the iliac graft, (5) the mandible graft is more effective, whereas (6) the cranium graft and (7) rib graft are less effective for alveolar cleft reconstruction. The efficacy of the remaining grafting materials was supported by insufficient evidence. More well-designed controlled studies are needed to ascertain the long-term clinical results of alveolar cleft reconstruction.

Key words: alveolar bone grafting; autograft; bone substitutes; cleft palate; tissue engineering.

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An alveolar cleft is a common congenital deformity with an incidence of 0.18–2.50 per 1000 births[1], and presents in approximately 75% of cleft lip and palate patients[2]. Genetic and environmental factors may cause incomplete fusion of the maxillary prominence and intermaxillary prominence, which results in an alveolar cleft[3,4]. The existence of an alveolar cleft may impact facial symmetry, development of the dentition, speech, and oral hygiene. Reconstruction of the alveolar process can stabilize the maxillary segments, close the oronasal fistulae, eliminate the nose asymmetry, and provide bony support for tooth eruption, orthodontic treatment, and the placement of dental implants[1,2,5].

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Since the first description of secondary alveolar bone grafting (SABG) by Boyne and Sands in the 1970s[6], it has become the most acknowledged method for the repair of alveolar clefts. SABG is usually performed at the mixed dentition stage, as it is believed that this will have minimal influence on maxillary growth. The iliac cancellous bone graft (ICBG) harvested from the anterior iliac crest has been the most common grafting material for the SABG procedure because of its abundance of bone, ease of harvest, and the ability to harvest simultaneously with alveolar cleft preparation[5].

Although the ICBG is considered the gold standard graft for the SABG procedure, it has some noted disadvantages. Donor site morbidity at the iliac crest is significant, such as postoperative pain, sensory disturbance, and claudication, and this results in a prolonged hospital stay[7]. There is also unavoidable bone absorption of the ICBG. It has been reported that the bone absorption rate could be more than 40% at 1 year after SABG[8], which may increase the need for reoperation.

Considering these shortcomings of the ICBG, alternative and supplementary grafting materials for SABG have been explored in a large number of studies. Transplantation of autogenous bone from other donor sites, for instance the cranium, mandibular symphysis, or tibia, may provide alternative choices with less donor site morbidity and a lower bone absorption rate than for the iliac crest[7]. Bone tissue engineering strategies, such as implanting bone scaffolds, growth factors, or autogenous cells, have also shown promising outcomes in repairing alveolar clefts and have the advantage of eliminating a second surgical site for bone harvesting[8]. Furthermore, because of the abundant growth factors and osteoinductive potential, tissue engineering strategies may increase bone retention and achieve a better alveolar reconstruction result than the ICBG[9].

This systematic review was conducted to compare the efficacy of alveolar bone reconstruction for alveolar cleft patients between the traditional iliac graft and alternative or supplementary bone grafting materials. The goal was to provide the clinician with options for use when selecting graft materials for alveolar cleft repair.

Materials and methods

The study selection, quality assessment, and data extraction processes were performed by two authors in duplicate, according to a protocol developed prior to the systematic review. The protocol has been registered in the PROSPERO database (CRD42014009942). Any disagreements were resolved by discussion.

Inclusion criteria

The inclusion criteria for this systematic review were as follows: (1) the study design was required to be a randomized controlled trial (RCT) or non-randomized controlled trial (N-RCT). Systematic reviews, review articles, case series, case reports, historically controlled studies, and case–control studies were excluded. (2) All participants had to be alveolar cleft patients undergoing SABG, including patients with a unilateral cleft or bilateral cleft. SABG was defined as receiving alveolar bone grafting at stages later than the primary dentition, including those undergoing surgery in the mixed dentition and mature dentition stages. Studies only assessing the results of alveolar bone grafting in the primary dentition were excluded. (3) The control group patients had to undergo SABG with ICBG transplantation. Studies whose control group received other types of autogenous bone graft were excluded. The intervention group had to undergo the transplantation of any other different grafting material for comparison with ICBG transplantation. (4) In terms of outcomes, the study was required to assess the efficacy of alveolar bone reconstruction. The required primary outcomes were (i) bone volume, measured using three-dimensional imaging modalities, and (ii) bone height, including the clinical success rate, the exact bone height, and the percentage of bone height formation/resorption. The required secondary outcomes were alveolar bone width/thickness and bone density. Studies that did not report the above outcomes were excluded.

Search strategy

The following electronic databases were searched without language limitation: MEDLINE (via OVID; 1948 to June 2016), Embase (via OVID; 1984 to June 2016), Cochrane Central Register of Controlled Trials (CENTRAL; issue 6, 2016), Chinese BioMedical Literature Database (CBM; 1978 to June 2016), and China National Knowledge Infrastructure (CNKI; 1994 to June 2016). Relevant journals and the reference lists of included studies were manually searched.

The search strategy combined medical subject heading (MeSH) terms with free text words. The MeSH terms used were ''Cleft Palate'', ''Cleft Lip'', ''Bone Transplantation'', and ''Ilium''. The titles and abstracts of all studies resulting from the search were initially screened to identify any eligible studies. The full texts of the possibly eligible studies were then obtained and a final judgement made.

Methodological quality assessment

All studies that met the inclusion criteria were evaluated against the 'treatment benefits' section of the *Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence*[10]. The evidence of 'treatment benefit' section is divided into five levels as follows: level 1 represents a systematic review of randomized trials or n-of-1 trials; level 2 represents a randomized trial or observational study with a dramatic effect; level 3 represents a non-randomized controlled cohort/follow-up study; level 4 represents case series, case–control studies, or historically controlled studies; level 5 represents mechanism-based reasoning. In this review, levels 1 and 2 were considered 'high methodological quality', whereas levels 3–5 were considered 'low methodological quality'.

Data extraction

The following data were extracted: investigators, study design and methodological quality, patient characteristics, interventions and controls, and outcomes. The patient characteristics extracted included the number of patients, types of cleft (if the study recruited only bilateral cleft patients, this was noted and a separate analysis was performed), and age at operation (if the mean age of the patients at operation was >16 years, this was noted specifically as 'skeletally mature' and a separate analysis was performed). If a single study reported both primary outcomes and secondary outcomes, only the primary outcomes were extracted and analyzed; if a single study reported only secondary outcomes, the secondary outcomes were extracted and analyzed.

Meta-analysis

The meta-analysis was performed using RevMan version 5.3 (Cochrane Collaboration). For continuous data (e.g., bone filling rate), mean differences (MD) with the 95% confidence intervals (CI) were calculated. For dichotomous data (e.g., clinical success rate), risk ratios (RR) with the 95% CI were calculated. The significance of the pooled MD and RR were