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Bone graft in posterior spine fusion for adolescent idiopathic scoliosis: a meta-analysis

Short Title

Graft options in posterior fusion for AIS

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Main text

Introduction

Adolescent idiopathic scoliosis (AIS) is one of the most common diseases among teenagers, with an overall prevalence of 0.47–5.2 % worldwide (1); many requiring surgical correction. Spinal fusion for idiopathic scoliosis was first described by Hibbs (2), and the addition of iliac crest bone graft (ICBG) to enhance fusion rates was implemented by Moe (3) in 1958. Patients undergoing the Moe technique of autologous ICBG and interfacet/intertransverse fusion without instrumentation were found to develop pseudarthrosis at a rate of 27.8% (3). Most authors suggest that loss of correction of more than 10° indicates possible instability or pseudarthrosis (4). The introduction of Harrington instrumentation in the 1980's decreased the rate of pseudoarthrosis to 18.1%, with a further reduction with the addition of autograft (5). Today the standard procedure is instrumentation and fusion of ten or more vertebrae with forceful correction of the deformity (6). Pseudarthrosis rates with this type of fixation have been reported to be as low as 0-3% with either allograft or autograft bone (7).

The type of supplemental graft material used to accomplish fusion in the posterior correction of AIS remains controversial. Autogenous bone grafting remains the "gold standard" for spine fusion (8), and is still performed by most surgeons in this patient population (9). The most common site for harvesting autograft is the iliac crest, although local graft and bone marrow aspirate are also used. With osteoconductive and osteoinductive properties, autograft has been shown to be a reliable material (10, 11). However, it has been reported that the use of autogenous bone graft is limited by the additional surgical time required to harvest the graft, increased blood loss, the morbidity associated with the donor site, and the limited availability of cancellous bone, especially in the paediatric age group (10, 12, 13). Because of this, interest has been focused on the alternatives, including allograft and bone substitutes (4, 7, 14, 15).

The use of allograft in the thoracolumbar spine in the adolescent population has shown similar fusion results to autograft with decreased morbidity, operation time, and blood loss (7, 9, 15-17). Additionally, several studies have documented the safety of freeze-dried allograft (18, 19), however, concerns regarding theoretical disease transmission, limited osteoinductive properties, and subsequent questions concerning the rate of successful arthrodesis have dampened some enthusiasm. A variety of other bone graft substitutes are also currently used in orthopaedics including bioactive ceramic granules, beta tricalcium phosphate, coralline hydroxyapatite, and osteogenic protein-1, with variable fusion success rates (20, 21).

To date there have been no meta-analyses in the literature comparing the use of autograft, allograft and bone substitutes to supplement posterior spinal fusion for AIS. We therefore have conducted a systematic and critical literature review with meta-analysis in order to determine any differences in fusion rates, intraoperative and postoperative complications.

Materials and methods

Search strategy and study selection

An electronic and manual literature review was conducted according to PRISMA (Preferred Reporting for Systematic Reviews and Meta-Analyses) guidelines for meta-analyses utilized to guide selection, appraisal, and quality of research (22). PubMed, EMBASE, Medline, Cinahl, and The Cochrane Library searches were conducted in January 2017 for articles published in English. As the anticipated the number of prospective randomised controlled trials (RCTs) to be small, relevant retrospective and prospective cohort studies (non-randomised) were included to increase the yield of information for 'best evidence synthesis'. The same search strings were used for each database, with slight modifications for the Cochrane database to take into account different search engines. Keywords "spine fusion" and its derivatives, in combination with "adolescent idiopathic scoliosis", and "autograft or allograft", were used to identify studies reporting on various bone graft options for posterior fusion in AIS.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) a randomized controlled trial (RCT), prospective or retrospective comparative study design (cohort or case-controlled studies) comparing various bone graft options during posterior spine fusion for AIS; (2) outcome measurements reported including fusion rate (3) English language; (4) 20 patients or more in each group; (5) at least 12-months follow-up. Articles that did not meet the inclusion criteria, including case reports and series, were ruled out.

Data extraction and quality assessment

After the removal of duplicates, all titles and abstracts were screened for relevance by two independent reviewers (NK and LH) according to inclusion and exclusion criteria. Irrelevant records were removed and the full texts of all remaining studies were reviewed for possible inclusion. Differences in judgment regarding inclusion or exclusion of studies were resolved through discussion to achieve consensus. In case of persistent disagreement, a third independent reviewer (AH) made the final decision. The references cited by each article were examined thoroughly to identify studies that were not retrieved from the initial search. Major orthopaedic and musculoskeletal journals were also searched to identify published studies that had not yet been indexed in the aforementioned databases. This protocol was repeated before submission to identify any studies that had been published during manuscript preparation.

Statistical analysis

Meta-analyses were performed using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). The program Metaan was used to analyse continuous outcomes whereas the program Metoprop was used for binary outcomes. Before evaluating the data, the researchers hypothesized that heterogeneity would exist between studies. To account for such differences, we used the I^2 statistic to determine the degree of variability between studies. I^2 values of 0%, >0%, 25%, 50%, and 75% were characterized as zero, very low, low, moderate, and high heterogeneity, respectively. A random effects model was used for heterogeneous data. A probability of p= 0.05 was considered to be statistically significant.

Results

Search results

The flow diagram of the search strategy is summarized in Fig. 1. A total of 216 articles were initially identified. The Pubmed database produced 80 hits whilst Medline, Embase, and Cinahl, using the same search strategy, produced 57, 62, and 16 hits, respectively. The Cochrane database revealed only 1 hit, which was excluded as it wasn't relevant to this review. From these 216 references, 179 were excluded as not relevant to this review based on title and abstract. A further 26 were eliminated upon further review based on full text review and not meeting inclusion criteria.

Demographic characteristics and quality assessment

The characteristics of included studies are presented in Table 1. Each included study was rated for its Level of Evidence as indicated by the July 2004 Journal of Bone & Joint Surgery guidelines (23). This meta-analysis included one level I LOE study, three level II LOE studies and eight level III LOE studies. Among all included studies, there was one RCT (24), three prospective randomised cohort studies (16, 25, 26) and eight retrospective cohort studies (9, 13, 17, 27-31).

Clinical outcomes

Fusion

Pseudoarthrosis was considered present with loss of correction of more than ten degrees. Based on the findings of the twelve included studies of 2389 patients included for analysis, there was no statistically significant difference in fusion rates between groups ($p<0.05$; Fig. 2). The groups included were autograft ICBG, autograft local, allograft, allograft/autograft combined, and bone substitute. The overall fusion rate was found to be 100% (95% CI 0.99 to 1.00; $I^2 = 48\%$).

Estimated blood loss

Eight studies included reports of total estimated blood loss (833 patients in the ICBG group and 1295 in the control group). Total EBL was significantly higher in the ICBG group (1018mls, 95% CI 859 to 1177) compared with control group (865mls, 95% CI 781 to 949) (p<0.01; I^2 = 91%; Fig. S1). Two studies had estimated blood loss but no information regarding standard error or deviation, hence were replaced by the largest standard error from the corresponding group (182ml in the ICBG and 102ml in the control group).

Operative time

Operative time obtained in eight studies (662 patients in the ICBG group and 1116 in the control group) was analyzed. The mean operative time was significantly higher in the ICBG group (259mins, 95% CI 237 to 282) compared with control group (237mins, 95% CI 217 to 257) (p<0.001; I^2 = 95%; Fig. S2).

Wound infection

Nine studies with a total of 1436 patients reported the data of wound infection. The pooled analysis indicated that there was no significant difference between groups in terms of wound infection (p = 0.6). The overall wound infection rate was found to be 1% (95% CI 0.0 to 0.02; I^2 = 36%).

Post-operative pain

Post-operative pain is the most common complication mentioned in the literature. Eight studies reported on post-operative pain (330 in the ICBG group and 619 in the control group). Post-operative pain defined as complaining of moderate to severe pain with need for medication at final follow-up. The percentage of patients with post-operative pain issues was significantly higher in the ICBG group (26%, 95%CI 0.17 to 0.37) compared with control group (9%, 95%CI 0.03 to 0.18) (p <0.001; I^2 = 92%).

Discussion

There is a paucity of clinical data comparing the use of bone graft options in AIS. Traditionally ICBG has been the “gold-standard”, however due to concerns over donor-site morbidity and low pseudoarthrosis rates reported with modern instrumentation independent of graft selection, alternatives such as allograft and bone graft substitutes are being considered. In a review by Xu et al. 2016 (32), it is suggested that allograft and ceramics exhibit similar benefits in achieving spine fusion to ICBG with no increase in pseudoarthrosis rate or surgical morbidities. However, there is no definitive evidence for or against ICBG harvesting to supplement posterior spinal fusion for AIS. Hence, an evidence-based meta-analysis is necessary to further clarify the pseudoarthrosis and complication rates of autograft, allograft and bone substitutes in posterior spinal fusion for AIS.

With the use of modern posterior segmental instrumentation with pedicle screws, current pseudoarthrosis rates have been reported to be less than 3% (7, 17, 24, 33), regardless of graft selection. Our meta-analysis showed no statistically significant difference in fusion rates between the groups with an overall fusion rate of 100%. Potential reasons for low pseudoarthrosis rates seen in grafts without osteoinductive properties include an increased fusion ability in the skeletally immature spine and a rigid fixation with pedicle screw instrumentation. There is also the possibility of metalware obscuring accurate assessment of pseudoarthrosis. Another consideration is that true bony fusion might not matter as long as there are no returns to surgery for instrumentation failure or loosening. Price et al. 2003 observed pseudoarthrosis rates between 15% and 25%, however only 2% of these cases required a new intervention due to persistence of pain or progression of the curve (33)

Donor-site morbidities are a consideration when crest harvesting is performed. Banwart et al. 1995 in a study of 261 patients having ICBG showed major complications in 10% of patients and minor complications in 39% (12). However, definitive evidence for or against ICBG harvesting in AIS surgery does not exist. Perioperative blood loss remains a concern and can lead to various clinical problems including increased risk of blood transfusion, longer hospital stays, and increased incidence of postoperative complications such as infection (34). Dhawan et al. 2006 showed average of 71mL additional blood loss associated with posterior ICBG harvesting during a posterior spine fusion procedure (35). In this meta-analysis, patients in the ICBG group had obviously greater blood loss averaging 153mL more compared with control group.

Operative time is an important parameter to evaluate surgical safety. In this meta-analysis the ICBG group had significantly longer operative times, averaging 22 minutes more than patients in the control group. Although increased operative time could be influenced by multiple confounding variables, there was no difference in the levels fused between groups. The results of this study are consistent with intuitive reasoning and with the measures from Dhawan et al. 2006 (35), who reported an average of 37 minutes additional surgical time with autogenous crest harvesting.

Persistent pain at the donor site is the most common complication of harvesting procedures (10, 12, 36). In a meta-analysis of 6449 patients on complications following autologous bone graft harvesting from the iliac crest, almost 10% of patients suffered from chronic donor-site pain (36). Our study showed post-operative pain issues were significantly higher in the ICBG group compared with the control group (16% versus 9%) at an average of 34-months follow-up. Donor site infection is also a much referenced morbidity of this procedure. Our study showed no significant difference in infection rate in ICBG compared to other groups with an overall infection rate of 1%. This is possibly due to the paediatric population who may be less predisposed to infection in this region due to better general health and soft tissue integrity, allowing more secure wound closure over the relatively subcutaneous posterior iliac crest.

Currently, the most common practice in our region (Melbourne, Australia) is the use of local autograft alone. Violas et al. 2004 first proposed using only local autologous bone graft in AIS posterior fusion with pedicle screw instrumentation and reported good outcomes with a follow-up period of 6 years (37). Our study included only two studies that employed the use of local autograft alone with an overall fusion rate of 100% (28, 30). In a direct comparison with ICBG, Mardomingo et al. (28) demonstrated that local autograft alone could achieve the same fusion rate whilst having shorter operative times and less blood loss. However, a statistically significant increase in loss of correction was observed in the local autograft alone group ($p = 0.02$). This was hypothesized to be due to the influence of more extensive releases required in obtaining local only graft, however further studies with longer follow-ups are needed to investigate this potential relationship.

This study has some limitations that must be taken into account. First, the majority of studies in this meta-analysis were prospective and retrospective comparative study designs, with only one RCT included. Without randomization it is very difficult to control for confounding variables, as there may have been patient and surgeon factors influencing results. Second, studies were performed in different surgical centers by varying levels of surgical expertise and operative techniques. Different surgical experience and measurement criteria are two main sources of clinical heterogeneity. Finally, post-operative activity protocols and pain medication regimens were not standardized between studies and follow-up duration ranged from between one and six years. Nevertheless, this meta-analysis was conducted by appropriate search strategies, strict inclusion and exclusion criteria and statistical methods.

The current meta-analysis found ICBG confers no advantage over the other graft options in achieving fusion in AIS surgery. Furthermore, crest harvesting was associated with significant increases in blood loss, operative time and post-operative pain issues. Hence, ICBG should be considered not so much the "gold standard", merely the "first standard" for fusion in AIS surgery, conferring no advantage. Furthermore, local autograft, allograft and bone substitutes are attractive alternatives to iliac crest grafting during posterior fusion in AIS.

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Disclosure statement

There is no relevant conflict of interests to declare and no funding was received for this study. The research didn't involve any human participants or animals and informed consent wasn't required.

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Figure legends

Figure 1. Algorithm demonstrating the process of study selection.

Figure 2. Forest plot of the fusion rates between allograft, autograft ICBG, autograft local, allograft/autograft combined, and bone substitute groups.

List of supporting information

Figure S1. Forest plot of the total estimated blood loss between the autograft ICBG and control groups.

Figure S2. Forest plot of the operative time between the autograft ICBG and control groups.

Figure S3. Forest plot of wound infection rates between allograft, bone substitute, local autograft, and autograft ICBG groups.

Tables

References	**Year**	**Study type (Level of evidence)**	**Total patients (graft)**		**Mean age (years)**		**Follow up time (months)**	
Fabry (17)	1991	Retrospective cohort study (III)	82 (ICBG)	98 (Allo)	14.1	14.6	12	12
Le Huec (29)	1997	Retrospective cohort study (III)	24 (Allo + local)	24 (TCP)	21	20	48	48
Ransford (26)	1998	Prospective randomised cohort study (II)	159 (ICBG)	168 (TCP)	15.9	16.2	18	18
Delecrin (14)	2000	Prospective randomised cohort study (II)	28 (ICBG)	26 (TCP)	17.5	18.2	49	48

Knapp (9)	2005	Retrospective study (III)	108 (Allo + local)		14.2		72	
Betz (24)	2006	RCT (I)	36 (Allo)		14.5		24	
Lerner (25)	2007	Prospective randomised cohort study (II)	20 (ICBG)	20 (TCP)	19.5	18.5	49	47
Ilharrebord e (13)	2008	Retrospective cohort study (III)	37 (ICBG)	47 (BG)	14.8	15.2	40	38
Crawford (31)	2013	Retrospective cohort study (III)	342 (ICBG)	563 (non-ICBG)	14.9	14.9	24	24
Mardoming o (28)	2013	Retrospective cohort study (III)	37 (ICBG)	36 (local)	15.1	14.4	126	66
Theologis (27)	2015	Retrospective cohort study (III)	151 (ICBG)	199 (Allo)	14.7	14.7	24	24
Yeh (30)	2016	Retrospective cohort study (III)	61 (local)		13.9		60	

Table 1 Characteristics of included studies. *ICBG* iliac crest bone graft, *Allo* Allograft, *TCP* tricalcium phosphate, *BG* bioactive glass, *RCT* randomized control trial