Allograft versus autograft for pediatric posterior cervical and occipito-cervical fusion: a systematic review of factors affecting fusion rates

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OBJECTIVE Fusion rates are high for children undergoing posterior cervical fusion (PCF) and occipito-cervical fusion (OCF). Autologous bone has been widely used as the graft material of choice, despite the risk of donor-site morbidity associated with harvesting the bone, possibly because very low fusion rates were reported with posterior allograft cervical fusions in children several decades ago. Higher overall fusion rates using allograft in adults, associated with improvements in internal fixation techniques and the availability of osteoinductive substances such as bone morphogenetic protein (BMP), have led to heightened enthusiasm for the use of bank bone during pediatric PCF. A systematic review was performed to study factors associated with successful bone fusion, including the type of bone graft used.

METHODS The authors performed a comprehensive PubMed search of English-language articles pertaining to PCF and OCF in patients less than 18 years old. Of the 561 abstracts selected, 148 articles were reviewed, resulting in 60 articles that had sufficient detail to be included in the analysis. A meta-regression analysis was performed to determine if and how age, fusion technique, levels fused, fusion substrate, BMP use, postoperative bracing, and radiographic fusion criteria were related to the pooled prevalence estimates. A systematic review of the literature was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

RESULTS A total of 604 patients met the specific inclusion and exclusion criteria. The overall fusion rate was 93%, with a mean age of 9.3 years and mean follow-up of 38.7 months. A total of 539 patients had fusion with autograft (94% fusion rate) and 65 patients with allograft (80% fusion rate). Multivariate meta-regression analysis showed that higher fusion rates were associated with OCF compared with fusions that excluded the occiput ($p < 0.001$), with the use of autograft instead of allograft ($p < 0.001$), and with the use of CT to define fusion instead of plain radiography alone. The type of internal fixation, the use of BMP, patient age, and the duration of follow-up were not found to be associated with fusion rates in the multivariate analysis.

CONCLUSIONS Fusion rates for PCF are high, with higher rates of fusion seen when autograft is used as the bone substrate and when the occiput is included in the fusion construct. Further study of the use of allograft as a viable alternative to autograft bone fusion is warranted because limited data are available regarding the use of allograft in combination with more rigid internal fixation techniques and osteoinductive substances, both of which may enhance fusion rates with allograft.

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KEY WORDS cervical; occipital; fusion; allograft; bone morphogenetic protein; pediatric; spine

AUTOLOGOUS bone has long been considered the “gold standard” bone source for posterior cervical fusion (PCF) in adult and pediatric patients, despite the fact that multiple studies over the past several decades have shown that allograft bone materials produce very high fusion rates in other parts of the spine, while

eliminating donor-site morbidity.^{46,50,62,138} While allogenic bone graft material does not offer the osteogenic, osteoinductive advantages of autograft, the use of allogenic bank bone has produced very high spinal fusion rates overall throughout the rest of the spine, particularly when rigid internal fixation techniques are used.^{93,114}

ABBREVIATIONS BMP = bone morphogenetic protein; FE = flexion and extension; IC = iliac crest; OCF = occipito-cervical fusion; PCF = posterior cervical fusion.

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The complications associated with the use of autograft are well known, including longer operative times, postoperative pain, increased blood loss, increased infection risk, seroma formation, pelvic fracture, the risk of peripheral nerve injury, and donor site pain, which can be long lasting.^{87,93,126} These complications are particularly troublesome in young children, making the use of allograft even more appealing in the pediatric population. These concerns, combined with the robust propensity for fusion in young children, led surgeons to embrace the concept of allograft use during PCF in the pediatric population once safe sources of allogenic bone became available many years ago.^{68,82,138}

Even though the use of allograft seems ideally suited for PCF in children, initial reports published over 30 years ago were associated with very low fusion rates.^{68,82,138} These disappointing early results with allograft alone, without autologous bone grafting, contributed to the widespread teaching of spine surgeons that PCF in children should be performed with autologous bone graft as the primary fusion substrate.^{46,50,62,138} However, more recently, surgeons have been emboldened to once again attempt to use allograft alone based on higher fusion rates associated with more rigid internal fixation techniques, the availability of osteoinductive substances such as bone morphogenetic protein (BMP), and the high fusion rates recently reported in adults who have undergone PCF using allograft alone.

We chose to perform a systematic review of the available medical literature related to fusion rates in patients less than 18 years of age who had undergone PCF, with or without inclusion of the occiput. Our primary objective was to determine the relative fusion rates using allograft compared with autologous bone graft, while also considering the effect of other study variables.

Methods

A literature search was performed using PubMed for English-language articles with the keywords “allograft,” “autograft,” “graft,” “atlantoaxial,” “occipito-cervical fusion,” “cervical instability,” “C1–2 instability,” “os odontoideum,” and “fusion.” The systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.¹³⁰ To be included in our analysis, the abstract needed to be in the English language and have information regarding PCF and/or occipito-cervical fusion (OCF). From this initial search, a total of 561 abstracts were selected, dating from January 1966 to July 2014. From these 561 abstracts, we selected 148 full-text articles for further review, selecting only those articles that may have had information regarding PCF or OCF in at least 1 patient who was less than 18 years of age.

Two authors (S.L.R., G.F.T.) independently reviewed each of the 148 journal articles. Articles were eliminated from consideration if they did not satisfy each of the inclusion criteria: information concerning PCF or OCF in at least 1 patient who was younger than 18 years of age, specific data regarding the fusion construct and fusion rates, the type of graft material used, and sufficient follow-up

for the authors of the articles to determine if a successful fusion had taken place. We included patients who had less than 1 year of follow-up if a successful fusion was documented. If follow-up was less than 1 year and no fusion was documented, we excluded that patient from the analysis. Papers that did not provide detailed information concerning all the inclusion criteria, such as technical notes or broad review papers without individual patient data, were excluded from the statistical review. If both reviewers agreed that a study met all the inclusion and exclusion criteria, the study was included in our analysis. If the reviewers disagreed, they reviewed the article together and made a joint decision about its inclusion. Eighty-eight articles did not meet the specific criteria for inclusion and were consequently excluded from this study. These articles are listed in Table 1.

Of the 148 articles reviewed, 60 articles met the inclusion criteria for a total of 604 patients included in the review. Many of the articles described a heterogeneous group of patients, with great variation within each paper regarding patient age, the method of internal fixation, the type of bone graft used, the method of postoperative external orthosis, and the radiographic method used for assessing fusion. For this reason, individual patient data were separated in a large data sheet to distinguish between patients with similar variables from those who were managed differently. For example, groups of patients within each article with similar fusion techniques, bone source, BMP use, postoperative orthosis, and method of radiographic follow-up were separated from those with dissimilar management strategies. By separating patients in this way, we could independently analyze each variable.

Data regarding age, internal fixation technique, graft type (autograft vs allograft), bone source, levels of fusion, the use of BMP, the type of postoperative orthosis, and the duration of follow-up were recorded. Two main groups were distinguished according to internal fixation techniques of the fusion construct: those who underwent nonrigid techniques and those who underwent more modern screw techniques. Onlay fusion and wiring were considered nonrigid constructs (primary wiring). Transarticular screws, screw/rod, and screw/plate internal fixation techniques were considered rigid constructs (primary screws).

Individual patient data regarding the bone substrate used was also documented. A fusion was considered done with autologous bone if bone graft was harvested and used for the fusion, with or without the use of allograft to supplement the fusion construct. A patient was considered in the allograft group if the fusion was done primarily with allograft bone material or bone substitutes, without separately harvesting autologous bone graft. Typical autologous bone graft sources included iliac crest (IC), skull, rib, spinous process, femur, or tibia/fibula. We considered allograft to include cancellous bone chips, freeze-dried cortical bone, or calcium hydroxyapatite.

The use of recombinant human BMP-2 was also recorded. If the use of BMP was not specifically stated in the article, we recorded “no” if the paper was published before 2001. If there was no mention of BMP use in a paper published after 2001, we contacted the authors to determine if they had used BMP or not. If clarification was

TABLE 1. Eighty-eight papers reviewed but eliminated from the systematic review because key data were missing

Ahmed et al., 2008	Hood et al., 2013
Ain et al., 2006	Hooley et al., 2006
Anakwenze et al., 2011	Jackson et al., 1999
Anderson et al., 2007	Jandali et al., 2011
Arkader et al., 2007	Kalra et al., 2007
Aryan et al., 2008	Kang et al., 2012
Bailey et al., 1969	Lee et al., 2012
Bisson et al., 2010	Lee et al., 1997
Bollo et al., 2012	Lekovic et al., 2006
Brockmeyer et al., 1995	Lementowski et al., 2010
Buttermann et al., 1996	Lubelski et al., 2014
Chamoun et al., 2009	Martus et al., 2011
Chen et al., 2005	Mummaneni et al., 2010
Couture et al., 2010	Nakagawa et al., 1997
Crostelli et al., 2009	Ni et al., 2012
Dede et al., 2013	Nockels et al., 2007
Deutsch et al., 2007	Pang et al., 2010
Dickerman et al., 2005	Pang et al., 2005
Dormans et al., 1995	Pang et al., 2007
Duhem et al., 2008	Parker et al., 2009
Dzenitis et al., 1966	Peng et al., 2011
Eleraky et al., 2000	Rao et al., 1990
Elliott et al., 201238	Robertson et al., 1998
Elliott et al., 201239	Rodgers et al., 1999
Elliott et al., 201440	Rodgers et al., 1997
Elliott et al., 201441	Roy et al., 1970
Fahim et al., 2010	Rozzelle et al., 2013
Fargen et al., 2011	Sakou et al., 1989
Fenoy et al., 2008	Sawin et al., 1998
Fielding et al., 1976	Shin et al., 2006
Fielding et al., 1987	Simsek et al., 2009
Fuchs et al., 2001	Steinmetz et al., 2003
Garg et al., 2003	Tauchi et al., 2012
Goel et al., 2013	Thomas et al., 2010
Govender et al., 2001	Tsirikos et al., 2007
Griswold et al., 1978	Tubbs et al., 2011
Hamblen et al., 1967	Tubbs et al., 2002
Hamilton et al., 2011	Tuli et al., 2004
Hardy et al., 1985	Vaccaro et al., 2002
Harrington et al., 2007	Wang et al., 2012
Hedequist et al., 2010	Wills et al., 2006
Hedequist et al., 2008	Yerramneni et al., 2011
Heilman et al., 2001	Zenonos et al., 2012
Heuer et al., 2009	Zhang et al., 2013
Hillard et al., 2009	

not possible by contacting the authors, we recorded BMP use as “presumed no” (designated by asterisk in Tables 2–4) if there was no mention of BMP use in a paper published after 2001.

Radiographic criteria and the assessment of fusion success varied and were not standardized among all studies. Imaging criteria determining successful fusion included plain radiographs, flexion and extension (FE) radiographs, and CT imaging. Successful reports of fusion were based on each author’s interpretation of the imaging results.

There is much variation in fusion criteria among authors, with earlier studies evaluating fusion with different methods from those of the recent literature. We qualified fusion based on the original author’s best assessment, regardless of imaging modality, whether it was plain radiography, FE radiography, or CT. Fusion rates were documented only when the article clearly stated that fusion was documented radiographically. All patients included in this review had a reported fusion status as “fused” or “not fused.”

Statistical Analysis

Statistical analyses were conducted using R version 3.0.0 (www.r-project.org), and a p value < 0.05 was considered statistically significant.¹¹⁵ We tested heterogeneity among study effect sizes with Cochran’s Q test and quantified heterogeneity by I^2 with $I^2 \leq 25\%$, $I^2 \approx 50\%$, and $I^2 \geq 75\%$ indicating low, medium, and high heterogeneity, respectively.⁶⁵ We used the fixed effects model to calculate pooled estimates and 95% CI for fusion prevalence because heterogeneity between studies was moderate ($I^2 = 26.9\%$).

Publication bias was assessed graphically using funnel plots and Egger’s regression asymmetry test. To further explore the sources of between-study heterogeneity, we performed a meta-regression analysis examining if and how fusion technique, levels fused, fusion substrate, BMP use, postoperative bracing, and radiographic fusion criteria were related to the pooled prevalence estimates. Factors that had a p value < 0.1 in the univariate analysis were included in a multivariate regression model.

Results

The detailed review of 60 full-text articles resulted in the analysis of 604 patients who underwent PCF or OCF before 18 years of age. Fifty-three papers described 539 patients who underwent PCF or OCF using autograft. Fourteen papers described 65 patients who underwent PCF or OCF using allograft, without autologous bone grafting (Fig. 1, Tables 2–6).

The data are presented in the tables and are stratified by fusion location (occipito-cervical vs cervical), fixation technique (primary wiring vs primary screw), and bone graft type (autograft vs allograft). Table 2 describes studies that evaluated OCF using autologous bone grafts; Table 3 summarizes papers that describe PCF (not including the occiput) with autologous bone graft, and Table 4 summarizes papers that describe patients who had OCF or PCF using allograft. Table 5 compares overall PCF and OCF rates with autologous bone graft versus allograft, with or without rigid fixation. Table 6 shows the results of our multivariate meta-regression analysis for the prevalence of pediatric patients who had a successful posterior OCF or PCF.

Posterior OCF Cohort

OCF performed with nonrigid internal fixation (primary wiring) was represented as follows: autologous bone was used in 188 patients described in 25 studies (Table 2); allograft was used in only 2 patients described in 2 studies (Table 4). OCF using rigid fixation (primary screw) was represented as follows: autologous bone was used in 135

FIG. 1. Flow diagram summarizing the literature review for the systematic review of published articles related to pediatric PCF. There is overlap in the number of articles in each category because articles frequently included patients with OCF and PCF and/or the use of allograft and autograft. Asterisks indicate that patients were stratified based on individual fusion construct, level, and material.

patients described in 15 studies (Table 2); allograft was used in 18 patients described in 5 studies (Table 4).

When nonrigid internal fixation was used for OCF, 179 (95%) of 188 patients who received autograft fused, but neither of the 2 patients in whom allograft was used successfully fused (0%) (Tables 2, 4, and 5). BMP was used in 48 (26%) of 188 of autograft, nonrigid OCF constructs, resulting in a 100% fusion rate. BMP was not used in either of the allograft, nonrigid OCF constructs, neither of which fused.

When more rigid internal fixation was used (primary screw) for OCF, 134 (99%) of 135 of patients fused with autograft and 17 (94%) of 18 fused with allograft (Tables 2, 4, and 5). The use of BMP with screw constructs, with autograft or allograft, resulted in a 100% fusion rate; BMP was used in 30 (22%) of 135 of the autologous, screw construct OCFs and in 13 (72%) of 18 of the allograft, screw construct OCFs.

The majority of OCFs were occiput–C2 fusions, but there were a few patients who had longer constructs (Tables 2 and 4). For the OCF cohort, autologous bone was harvested most commonly from the IC, but a wide variety of donor sites were reported. Most allograft was morselized cancellous bone, but some surgeons used synthetic materials. Halo bracing was used in a majority of OCFs done with nonrigid internal fixation while it was used in a minority of patients who had rigid internal fixation.

The average follow-up was generally long, with an average range of 12 to 39 months in the various cohorts (Tables 2 and 4).

PCF

PCF (not including the occiput) performed with nonrigid fixation (primary wiring) was represented as follows: autologous bone was used in 154 patients in 17 studies (Table 3); allograft was used in 11 patients described in 6 studies (Table 4). PCF using rigid internal fixation (primary screw) was represented as follows: autologous bone was used in 62 patients described in 15 studies (Table 3); allograft was used in 34 patients described in 5 studies (Table 4).

When nonrigid internal fixation was used for PCF, 134 (87%) of 154 patients who received autologous bone graft fused but only 4 (36%) of 11 who received allograft successfully fused (Tables 3–5). Two patients underwent nonrigid PCF with BMP, one each in the autograft and allograft groups, both of whom fused.

When rigid internal fixation was used, 61 (98%) of 62 fused with autologous bone graft and 31 (91%) of 34 fused with allograft (Tables 3–5). BMP was not used in any of the patients with rigid PCF who received autologous bone graft. However, BMP was used in 85% of rigid PCF cases with allograft: 5 of 5 (100%) cases that did not receive BMP fused; fusion was achieved in 26 (90%) of 29 patients who did receive BMP.

TABLE 2. Pediatric posterior OCFs using autologous bone graft

Authors & Year	No. Pts	No. Fused	% Fused	Mean Age (yrs)	Graft	Levels	BMP	Postop Brace (no. pts)	Fusion Criteria
OCF, autograft, primary wiring									
Holmes & Hall, 1978	4	4	100	6	IC	O-C3	N	RC, halo	FE
Koop et al., 1984	8	7	88	9	IC	O-C2, O-C3	N	Halo	FE
Flint & Hockley, 1987	5	5	100	8	IC	O-C3, O-C4	N	None	PR
Letts & Slutsky, 1990	7	7	100	9	IC	O-C3, O-C4	N	Halo	PR
Segal et al., 1991	6	4	67	10	N/A	O-C2 (3), O-C3 (2), O-C4 (1)	N	RC, halo	PR
Chadduck & Boop, 1994	5	4	80	11	S	O-C	N	RC, halo	FE
Casey et al., 1995	7	7	100	8	S	O-C	N	Halo	PR
Dormans et al., 1995 ³³	16	15	94	10	IC	O-C2, O-C3	N	Halo	PR
Higo et al., 1995	4	4	100	7	IC	O-C2	N	RC	PR
Doyle et al., 1996	1	1	100	12	IC	O-C2	N	Halo	PR
Tuite et al., 1996	16	16	100	12	IC, S, femur, fibula	O-C	N	None (5), RC (2), halo (9)	CT
Lowry et al., 1997	4	3	75	9	IC	O-C	N	Halo	FE
Schultz et al., 2000	13	12	92	8	IC, R	O-C	N*	RC (7), halo (6)	FE
Cohen et al., 2001	1	1	100	2	R	O-C2	N	Halo	PR
Houle et al., 2001	2	2	100	11	R	O-C	N	RC	PR
Meyer et al., 2001	2	2	100	6	IC	O-C2	N	Halo	FE
Rahimi et al., 2003	2	2	100	12	R	O-C2	N*	None	PR
Kim et al., 2004	11	11	100	9	N/A	O-C	N	RC (7), halo (4)	FE
Hosalkar et al., 2005	4	4	100	8	IC, R	O-C	N*	Halo	PR
Yamazaki et al., 2006	1	1	100	7	IC	O-C	N	Halo	PR
Moorthy et al., 2009	14	14	100	13	IC, R	O-C	N*	SC	FE
Visocchi et al., 2009	6	5	83	10	IC	O-C	N	RC (3), halo (3)	CT
Lindley et al., 2011	47	47	100	11	IC, R, S	O-C	Y	RC, halo	FE
Benzel et al., 2012	1	1	100	1	R	O-C2	Y	RC	CT
Pakkasjärvi et al., 2013	1	0	0	5	IC	O-C	N	Halo	PR
Total	188	179	95	9.8					
OCF, autograft, primary screws									
Brockmeyer & Apfelbaum, 1999	10	10	100	9	IC	O-C2	N	N/A	CT
Meyer et al., 2001	1	1	100	15	IC	O-C2	N	RC	FE
Anderson et al., 2006	9	9	100	5	IC, R	O-C2	N	N/A	FE
Jea et al., 2007	2	2	100	6	IC	O-C	N	RC	CT
Haque et al., 2009	4	4	100	9	R, S	O-C3	Y	RC	FE
Hankinson et al., 2010 ⁵⁶	73	73	100	8	IC, R	O-C2	N	RC (59), none (3), halo (11)	CT
Hankinson et al., 2010 ⁵⁷	2	2	100	13	IC	O-C	N	RC	CT
Hedequist et al., 2010	2	2	100	8	IC	O-C	Y	Halo	CT

(continued)

TABLE 2. Pediatric posterior OCFs using autologous bone graft (continued)

Authors & Year	No. Pts	No. Fused	% Fused	Mean Age (yrs)	Graft	Levels	BMP	Postop Brace (no. pts)	Fusion Criteria
OCF, autograft, primary screws (continued)									
Jeszczynski et al., 2010	1	1	100	11	IC	O-C1	N*	Halo	PR
Bauman et al., 2011	2	2	100	12	S	O-C	N	Halo	CT
Lindley et al., 2011	1	1	100	11	IC, R, S	O-C	Y	N/A	FE
Sribnick et al., 2012	20	20	100	9	R	O-C	Y (2)	RC (18), halo (2)	FE
Pakkasjärvi et al., 2013	3	2	67	11	IC	O-C	N	Halo	PR
Tauchi et al., 2012	1	1	100	6	IC	O-C3	N*	Halo	CT
Kosnik-Infinger et al., 2014	4	4	100	11	L	O-C	Y	RC	CT
Total	135	134	99	8					

FE = flexion and extension radiography; L = local bone graft; N = no; N/A = not available; O = occiput; PR = plain radiography; Pts = patients; R = rib; RC = rigid collar; S = skull; Y = yes.

* The use or lack of use of BMP was not explicitly stated, therefore presumed "no."

The vast majority of PCFs were C1–2 fusions, with a few patients undergoing fusion at lower cervical levels. Autologous bone grafts were generally structural grafts, harvested most commonly from the IC or ribs. Allograft used for PCF was often structural, but some authors used morselized cancellous chips or synthetic hydroxyapatite granules. Halo bracing was used in the majority of patients who underwent nonrigid internal fixation, but it was only used in 2 (2%) of 96 patients who had rigid constructs. The average follow-up in each cohort was long, ranging from 15 to 73 months (Tables 3 and 4).

Meta-Regression of the Entire Cohort

Fusion outcomes were stratified across various factors of interest to identify potential predictors of successful fusion (Table 6). Univariate meta-regression analysis of the entire cohort showed that the following factors were positively associated with a successful fusion, with p values < 0.1 : the use of autologous bone graft compared with allograft ($p < 0.001$), OCF compared with PCF ($p < 0.001$), rigid internal fixation compared with nonrigid fixation ($p = 0.02$), fusion defined by CT compared with plain radiography ($p < 0.001$), and a shorter follow-up duration ($p = 0.07$). Patient age, the use of BMP, and the method for bracing after surgery were not associated with successful fusion (Table 6, middle columns).

The following factors were independently associated with successful fusion in multivariate analysis: the use of autologous bone graft compared with allograft (regression coefficient = -0.13 , 95% CI = -0.20 to -0.05 , $p = 0.001$), OCF compared with PCF (regression coefficient = -0.07 , 95% CI = -0.11 to -0.03 , $p < 0.001$), and fusion defined by CT compared with plain radiography (regression coefficient = -0.10 , 95% CI = -0.17 to -0.03 , $p = 0.005$). The type of internal fixation and the duration of follow-up were correlated with fusion in the univariate analysis, but they had no correlation with fusion in the multivariate analysis (Table 6, columns on right).

Meta-Regression of OCF Subset

Subset analysis of only patients who underwent OCF showed similar trends as the overall cohort. Univariate analyses showed that patients who had fusion defined by CT were more likely to fuse than those who were assessed by plain radiography alone (regression coefficient = -0.1 , 95% CI = -0.17 to -0.04 , $p = 0.003$). Patients who received allograft were less likely to achieve fusion (regression coefficient = -0.1 , 95% CI = -0.21 to -0.01 , $p = 0.06$). Univariate analysis also showed that the type of internal fixation, use of BMP, method of bracing, age, and duration of follow-up were not associated with successful fusion ($p > 0.1$).

Multivariate analysis, using factors with $p < 0.1$ in the univariate analysis, showed that patients studied only with plain radiography were less likely to achieve fusion (regression coefficient = -0.11 , 95% CI = -0.18 to -0.04 , $p = 0.002$). Multivariate analysis of the OCF subset also showed that the use of allograft was also less likely to achieve successful fusion (regression coefficient = -0.1 , 95% CI = -0.21 to 0.004 , $p = 0.06$), but the result was not statistically significant.

TABLE 3. Pediatric PCFs (excluding the occiput) using autologous bone graft

Authors & Year	No. Pts	No. Fused	% Fused	Mean Age (yrs)	Graft	Levels	BMP	Postop Brace (no. pts)	Fusion Criteria	FU (mos)
PCF, autograft, primary wiring										
McWhorter et al., 1976	6	5	83	6	R	C1-3, C1-4	N	Halo	PR	85
Holmes & Hall, 1978	17	17	100	12	IC	C1-2 (8), subaxial (8), C1-subaxial (1)	N	RC (4), SC (8), halo (5)	FE	33
Koop et al., 1984	5	5	100	14	IC, R	C1-2 (4), C3-5 (1)	N	Halo	FE	56
Stabler et al., 1985	4	4	100	11	IC	C1-2	N	RC	PR	36
Mah et al., 1989	14	14	100	12	IC	C1-2	N	SC	FE	57
Segal et al., 1991	3	0	0	7	N/A	C1-2 (2), C1-3 (1)	N	RC (1), halo (2)	PR	23
Smith et al., 1991	17	15	88	N/A	IC, R	C1-2, C1-3	N	RC (7), halo (10)	FE	25
Chaddock & Boop, 1994	7	7	100	11	S	C1-2 (2), C4-5 (2) C1-3 (2), C4-7 (1)	N	RC (5), halo (2)	FE	24
McGrory & Klassen, 1994	31	24	77	13	IC, T	C1-2 (9), subaxial (19), C1-subaxial (3)	N	RC (22), halo (9)	FE	210
Doyle et al., 1996	8	4	50	8	IC	C1-2	N	Halo	PR	142
Lowry et al., 1997	21	18	86	9	IC	C1-2	N	RC (1), halo (20)	FE	13
Heilman et al., 2001	1	1	100	4	IC	C6-7	N	Halo	PR	36
Meyer et al., 2001	4	4	100	8	IC	C1-2	N	RC (2), halo (2)	FE	26
Parisini et al., 2003	12	12	100	11	IC	C1-2	N	Halo	FE	18
Oluigbo & Solanki, 2008	1	1	100	2	S	C1-2	Y	Halo	PR	3
Menezes, 2008	1	1	100	6	R	C1-3	N*	N/A	PR	48
Pakkasjärvi et al., 2013	2	2	100	6	IC	C1-2	N	Halo	PR	42
Total	154	134	87	10.5						73
PCF, autograft, primary screw										
Wang et al., 1999	13	13	100	10	IC, S	C1-2	N	RC	FE	26
Sasaki et al., 2000	1	1	100	5	IC, R	C1-2	N	SC	FE	12
Meyer et al., 2001	4	4	100	14	IC	C1-2	N	RC	FE	17
Brockmeyer, 2002	2	2	100	1	R	C1-2	N	N/A	CT	9
Rahimi et al., 2003	1	1	100	14	R	C1-2	N*	RC	PR	3
Anderson et al., 2006	8	8	100	5	IC, R	C1-2	N	N/A	FE	26
Beiner et al., 2006	1	1	100	10	IC	C3-5	N	RC	FE	36
Leonard & Wright, 2006	2	2	100	16	IC	C1-2	N	RC	CT	24
Jea et al., 2007	1	1	100	7	IC	C1-2	N	RC	CT	4
Haque et al., 2009	11	11	100	10	R, S, L	C1-2	N	RC	FE	15
Desai et al., 2010	1	1	100	9	IC	C1-2	N	RC	FE	23
Plant & Ruff, 2010	1	0	0	13	IC	C1-2	N*	N/A	FE	36
Bauman et al., 2011	10	10	100	11	S	C1-2 (7), C4-6 (2), C2-5 (1)	N	RC (9), halo (1)	CT	19
Pakkasjärvi et al., 2013	1	1	100	8	IC	C1-2	N	Halo	PR	48
Tauchi et al., 2013	5	5	100	11	IC	C1-2	N*	RC	CT	66
Total	62	61	98	9.6						24

FU = follow-up; SC = soft collar; T = tibia.

* The use or lack of use of BMP was not explicitly stated, therefore presumed "no."

TABLE 4. Pediatric posterior OCFs and PCFs using only allograft

Authors & Year	No. Pts	No. Fused	% Fused	Mean Age (yrs)	Graft	Levels	BMP	Postop Brace (no. pts)	Fusion Criteria	FU (mos)
OCF, allograft, primary wiring										
Koop et al., 1984	1	0	0	5	Cadaver R	O-C2	N	Halo	PR	49
Stabler et al., 1985	1	0	0	10	Cadaver R, I, F	O-C4	N	Halo	FE	23
Total	2	0	0	8						36
OCF, allograft, primary screw										
Belen et al., 2006	1	1	100	9	Chips of cancellous allograft	O-C2	N*	RC	N/A	12
Jea et al., 2007	1	1	100	2	IC (very small amount) & allograft	O-C	Y	RC	CT	4
Hankinson et al., 2010 ⁵⁷	2	2	100	13	Chips of cancellous allograft	O-C2	Y	Halo	CT	14
Hwang et al., 2012	10	10	100	9	Morselized allograft	O-C	Y	RC	CT	12
Ji et al., 2013	4	3	75	11	Synthetic bone substitute granules	O-C2	N*	RC	CT	12
Total	18	17	94	9.5						12
PCF, allograft, primary wiring										
Holmes & Hall, 1978	1	0	0	14	N/A	C1-2	N	RC	FE	32
Stabler et al., 1985	6	0	0	11	Cadaver R, I, F	C1-2 (5), C4-T1 (1)	N	RC (3), SC (1), halo (2)	FE	15
Stevenson et al., 2002	1	1	100	13	N/A	C1-2, C2-4	N	Halo	FE	36
Visocchi et al., 2009	1	1	100	12	Deantigenated heterologous bone graft	C1-2	N	RC	CT	46
Leng et al., 2010	1	1	100	15	Silicon-substituted calcium hydroxyapatite	C4-7	N*	RC	FE	12
Hwang et al., 2012	1	1	100	6	Morselized allograft	C1-2	Y	N/A	CT	15
Total	11	4	36	11.6						21
PCF, allograft, primary screw										
Gluf et al., 2005	1	1	100	N/A	N/A	C1-2	N*	RC	CT	36
Desai et al., 2010	7	7	100	9	Cadaveric cancellous bone chips	C1-C2 (5), C1-C3 (2)	Y	RC	PR	23
Hwang et al., 2012	20	17	85	8	Morselized allograft	C1-2	Y	RC	CT	12
Hood et al., 2013	2	2	100	5	Structural allograft or chips	C1-2	Y	RC	CT	23
Ji et al., 2013	4	4	100	9	Synthetic bone substitute granules	C1-2	N*	RC	CT	12
Total	34	31	91	7.7						15

F = femur; I = ilium.

* The use or lack of use of BMP was not explicitly stated, therefore presumed "no."

Meta-Regression of PCF Subset

Subset analysis of only patients who underwent PCF showed similar results to the OCF subset analysis; however, the effect of allograft use was more pronounced. The following factors were found to have a negative association with successful fusion ($p < 0.1$) and were subsequently used in the multivariate analysis: use of allograft (regression coefficient = -0.15 , 95% CI = -0.25 to -0.05 , $p = 0.002$) and the use of plain radiography instead of CT or FE radiography to determine fusion (regression coefficient = -0.14 , 95% CI = -0.27 to -0.01 , $p = 0.04$). The type of internal fixation, use of BMP, type of bracing, age, and duration of follow-up were not correlated with successful fusion ($p > 0.1$).

Multivariate analysis, using the aforementioned factors with a $p < 0.1$ in the univariate analysis, showed similar findings: patients with allograft (regression coefficient = -0.15 , 95% CI = -0.25 to -0.03 , $p = 0.01$) and for whom plain radiography was used to define fusion (regression coefficient = -0.16 , 95% CI = -0.3 to -0.03 , $p = 0.02$) were less likely to experience a successful fusion.

Publication Bias

A funnel plot and Egger's test were used to assess the potential publication bias for all of the studies included in the review. The asymmetrical shape of the funnel plot (Fig. 2) and the result of the Egger's test for funnel plot asymmetry ($p < 0.001$) suggest that publication bias may exist.

Discussion

The Effect of the Levels Fused, Type of Bone Graft, and Method of Internal Fixation

Our literature review confirms that fusion rates after OCF and PCF are high, except when fusion is performed using allograft and internal fixation that does not use screw constructs. The overall fusion rate for all OCF and PCF was 93%, with OCF having a higher fusion rate than PCF (96% vs 88%). The overall fusion rate for all OCF and PCF was also higher in the patients who received autologous bone graft compared with those in whom allograft was used (94% vs 80%). Similarly, fusion rates with autologous bone graft were higher than when allograft was used when comparative rates for OCF (97% vs 85%) and PCF (90% vs 78%) were considered separately.

The use of rigid internal fixation also improved fusion rates, albeit to a lesser extent than the type of bone graft used: screw fixation was associated with higher fusion rates than nonrigid fixation in both OCF (99% vs 94%) and PCF (96% vs 84%). However, the most dramatic discrepancy in fusion rates was observed when comparing fusion rates when allograft was used in combination with nonrigid internal fixation: successful fusion was much higher when autograft was used with nonrigid fixation in both OCF (95% vs 0%) and the PCF (87% vs 36%). However, fusion rates when allograft was used in combination with rigid internal fixation were only slightly lower in both the OCF (99% vs 94%) and the PCF (98% vs 91%) subgroups. Similarly, our review for the entire cohort showed that higher fusion rates were associated with fusions done with autologous bone and in those that included the occiput.

TABLE 5. Summary of the literature review comparing overall fusion rates for OCF and PCF stratified by the type of internal fixation and the bone type*

Fusion Type	Autograft	Allograft	Combined Autograft & Allograft
OCF			
Primary wiring	179/188 (95)	0/2 (0)	179/190 (94)
Primary screw	134/135 (99)	17/18 (94)	151/153 (99)
Total OCF	313/323 (97)	17/20 (85)	330/343 (96)
PCF			
Primary wiring	134/154 (87)	4/11 (36)	138/165 (84)
Primary screw	61/62 (98)	31/34 (91)	92/96 (96)
Total PCF	195/216 (90)	35/45 (78)	230/261 (88)
Overall totals	508/539 (94)	52/65 (80)	560/604 (93)

* Values are presented as number/total patients (%).

The findings of this review confirm that OCF and PCF in the pediatric population result in high overall fusion rates, particularly when screw-based internal fixation methods are used. Numerous studies have demonstrated the clear benefit of screw-based internal fixation techniques in adults and children, resulting in a significant reduction in the use of halo immobilization after surgery, and superior fusion rates compared with nonrigid internal fixation techniques.^{5,17,43,62,73} Improved surgeon familiarity with internal fixation techniques, combined with advancements in imaging, surgical planning, and the ease of use of spinal instrumentation devices, have led to the widespread use and acceptance of screw-based internal fixation techniques in both adults and children.

While there is now little debate regarding the advantages of rigid internal fixation, there is no consensus on whether allogenic bone graft should be used alone as the fusion substrate, without harvesting autologous bone graft.^{67,69,73,93} The use of autograft has long been considered the "gold standard" for OCF and PCF in children, and its use continues to be advocated by many surgeons.^{1,50,58,67,150} As recently as 2005, authors have considered the use of onlay allograft to be inappropriate for OCF.⁵⁰ When viewed in the context of modern bone grafting techniques throughout the rest of the spine, where allograft and bone substitutes have been used with high fusion rates, reduced donor-site morbidity, and minimal complications, this preference for the use of autologous bone with OCF and PCF seems paradoxical. It is possible that this bias originated 30 years ago, based on surprisingly poor fusion rates in children with OCF and PCF who underwent allograft fusions, when the concept of bank bone use for spinal fusions started gaining traction.^{68,82,138}

In 1984, Koop et al. noted that all of their pediatric OCF procedures performed with autologous bone resulted in fusion, whereas no fusion occurred in the 1 patient who received the allograft, leading the authors to recommend the use of autologous bone graft.⁸² A year later, Stabler et al. published an influential and frequently cited report of a 100% nonunion rate in 7 children who underwent PCF

TABLE 6. Univariate and multivariate fixed-effects meta-regression analysis for the prevalence of pediatric patients who had a successful posterior OCF or subaxial PCF

Variable	Univariate Analysis				Multivariate Analysis			
	Change in Prevalence	LCL	UCL	p Value	Change in Prevalence	LCL	UCL	p Value
OCF	Ref							
PCF	−0.1	−0.13	−0.06	<0.001	−0.07	−0.11	−0.03	<0.001
Internal fixation method								
Rods/screws	Ref				Ref			
Wire/cable/hook/onlay	−0.03	−0.06	−0.005	0.02	−0.02	−0.06	0.03	0.5
Bone source for fusion								
Autograft	Ref				Ref			
Allograft	−0.16	−0.23	−0.09	<0.001	−0.13	−0.2	−0.05	0.001
BMP								
N	Ref							
Y	0.02	−0.01	0.06	0.13				
N presumed	−0.04	−0.1	0.03	0.26				
Neck bracing after surgery								
None	Ref							
Rigid collar	0.06	−0.07	0.2	0.37				
Soft collar	0.05	−0.1	0.2	0.51				
Halo	−0.03	−0.17	0.1	0.63				
Criteria for fusion								
CT	Ref				Ref			
FE	−0.03	−0.05	0.003	0.08	0.01	−0.04	0.05	0.8
PR	−0.14	−0.2	−0.08	<0.001	−0.1	−0.17	−0.03	0.005
Age	−0.001	−0.007	0.005	0.75				
FU duration	−0.0005	−0.0009	−0.00001	0.07	−0.0002	−0.0008	0.0004	0.57

LCL = lower control limit; Ref = reference; UCL = upper control limit.

using cadaveric bone graft and wiring.¹³⁸ Based on our review of the literature, 23 years passed before there was another published article regarding OCF using allograft in children following Koop's publication, and 17 years passed before another article described allograft use for PCF in children following Stabler's article.^{11,82,138,140}

While there was a dearth of publications related to the use of allograft in pediatric cervical spine fusions for the 2 decades that followed the early failures reported in the 1980s, there has been a resurgence in interest over the most recent decade corresponding to the widespread use of rigid internal fixation techniques and the availability of BMP.^{56,69,73,78,88,151} Emboldened by the greater fusion rates associated with screw-based constructs, with or without the use of BMP, there has been a sharp rise in publications describing OCF and PCF in children and adults. Our review confirmed that fusion rates greater than 90% have been routinely reported with pediatric OCF and PCF when allograft is used with rigid internal fixation. This is in stark contrast to the very low fusion rates originally reported when less rigid internal fixation techniques were reported in the 1980s.^{68,82,138}

We are unaware of any large pediatric series that directly compares fusion rates using autologous bone versus allograft for OCF or PCF. However, there is emerging evidence that similar fusion rates can be achieved using al-

lograft in adult patients undergoing PCF. In a recently published meta-analysis of more than 1,000 adult patients who underwent a rod and screw posterior C1–2 fusion, Elliott et al. found that the fusion rate using allograft was very similar to that achieved with autograft (100% vs 99.7%).⁴⁰ Similarly, in a series that predominantly described PCF in adults with screw/rod constructs, Hood et al. reported a 100% fusion rate in 52 patients when BMP and allograft were combined.⁶⁹ Similar fusion rates have been reported for OCF in adult patients using allograft as well.¹⁰⁴ The findings of these large adult series confirm the trend seen in the pediatric literature: the use of allograft for OCF and PCF results in high fusion rates when combined with rigid internal fixation, with or without the use of BMP.³⁹

The Role of BMP in Allograft Fusions

As described in the section above, surgeons caring for pediatric and adult patients are more frequently utilizing allograft during OCF and PCF, and they achieve high fusion rates when rigid internal fixation is used.^{39,73} While these results suggest that allograft bone may serve as an adequate fusion substrate in this surgical scenario, the frequent use of BMP with allograft confounds the argument that allograft alone is sufficient to result in fusion. Many reports of successful OCF and PCF with allograft in adults

FIG. 2. Funnel plot of the Egger's test results showing an asymmetrical shape ($p < 0.001$) suggests that publication bias may exist.

also used BMP to promote fusion.^{39,69} Similarly, BMP was combined with allograft in the vast majority of OCF and PCF, resulting in successful fusion that we report in this review. Interestingly, the use of BMP was not statistically correlated with successful fusion in any of our univariate or multivariate analyses, when evaluating all OCF and PCF cases collectively or separately. However, the use of autograft was associated with a higher fusion rate than allograft in most of our analyses. These findings beg the question as to the necessity of BMP when allograft is used in conjunction with rigid internal fixation. While it is comforting to the surgeon to supplement allograft fusion with BMP, a substance that provides the osteoinductive properties that allograft is missing, is it necessary?

Questions regarding the necessity of BMP are not trivial considering the apprehensions that have been raised about the short- and long-term risks of utilizing BMP. In fact, the FDA recently issued a warning against the routine use of BMP in patients under 18 years, because its safety and effectiveness have not been reviewed or approved in this population.¹⁴⁹ Clearly, while multiple reports have shown that BMP can enhance spinal fusion rates, its use comes at a price.^{19,42} While an extensive recent administrative database review of short-term complications in pediatric spinal fusions failed to demonstrate a higher complication rate when BMP was used, the authors emphasize that caution should be used in interpreting this data based on the duration of follow-up and the limitations of their study.¹¹⁹ BMP is expensive, and its use has been associated with swelling, seroma formation, hematoma, ectopic bone formation, osteomyelitis and bone resorption, dysphagia, and breathing difficulties.^{20,91,93,130,132,136} Our analysis suggests that rigid internal fixation techniques may play a more important role than BMP in promoting fusion when allograft is used; however, our conclusions are limited by the small sample sizes reported and the limitations inherent in a retrospective review of the literature.

Other Variables Studied Predicting Successful OCF and PCF

Our analyses consistently showed that the assessment of fusion with static cervical plain radiography and shorter follow-up were associated with a lower fusion rate. We believe this association can be explained by the very nature of patient assessments after surgery and the era during which the studies were performed. While CT and FE radiography are now considered the optimal methods by which to assess fusion, CT was not available for patient assessment in early reports, when fusion rates were lower. Also, if static radiographs fail to demonstrate fusion, it is unlikely that clinicians would subsequently order dynamic studies, for fear of causing neurological compromise when the neck is manipulated. Lower fusion rates with longer follow-up can be accounted for by the fact that patients who experience failure to fuse often go on to other procedures, thereby extending their follow-up after the index operation.

Patient age also did not correlate with fusion rates in any of the analyses, a finding that is not surprising in pediatric patients, who generally exhibit a strong propensity to fuse. Based on the knowledge that rigid internal fixation improves fusion rates, it is possible that a larger study involving infants in whom rigid internal fixation is not possible might produce lower fusion rates. There was scant information pertaining to very young children reported in any of the papers we reviewed for this analysis.

The method of bracing after surgery also did not correlate with fusion rates. Halo immobilization was much more frequently used when nonrigid internal fixation was performed, but fusion rates were still relatively high. The majority of patients who underwent rigid internal fixation used a cervical collar or no external bracing at all after surgery.

Study Limitations

This study has all the major limitations of a retrospective literature review and, as a result, is subject to the inherent shortcomings of such manuscripts. All conclusions from this review are based on Class III data. We could not independently assess the quality of the surgical technique, the completeness of the follow-up, or the overall quality of the individual studies. The description of the operative technique in each article was often limited, particularly in regard to the precise fusion technique performed and whether BMP was used. Eighty-eight papers were eliminated from the review because they did not meet the inclusion criteria, but the description of the operative details was often scant in some of the articles that were included in the analysis. Judgments were made about whether a fusion was an allograft or autograft based on the written description in the manuscript. Also, judgments were made about whether a fusion was successful based on radiographic criteria. In many of the earlier manuscripts, CT was not available to identify fusion. Even in more recent studies, CT was not routinely used to assess fusion mass, even though CT is considered by many to be the standard imaging modality to define fusion.

Many of the studies in our review have a heterogeneous population and treated a wide variety of pathologies, which

we did not include in our analysis because the documentation was inconsistent. Additionally, inconsistent documentation of several of our other study variables inevitably skews our results and interpretation. It is also possible that authors are more likely to report successful fusions rather than failed fusion in the literature. Lastly, authors who had produced multiple studies could potentially report a single patient in several manuscripts, which leads to repetition of data.

Finally, it would have been ideal to subdivide the patients into 3 homogenous groups (OCF, C1–2 fusion, and subaxial PCF), because we suspect that C1–2 fusion rates would have been higher than subaxial fusion rates. However, many important papers from 30 to 40 years ago, when longer constructs were more common, failed to separate the results so precisely. We suggest that future studies on this topic further stratify the data to separate subaxial PCF from pure C1–2 fusions.

Conclusions

OCF and PCF result in high overall fusion rates in pediatric patients, regardless of whether autologous bone or allograft are used as the fusion substrate. Initial enthusiasm for allograft fusion 30 years ago, before more rigid internal fixation methods were developed, was dampened by very poor fusion rates when allograft was used without autologous bone grafting. More modern rigid internal fixation techniques have resulted in high fusion rates and a substantial reduction in the use of halo orthosis after surgery. Our meta-regression of published data over the past 50 years shows that fusion rates were higher with OCF than PCF and that autologous bone was more likely to lead to successful fusion than allograft. However, studies published in the past decade show that high fusion rates can be expected when rigid internal fixation is combined with the use of allograft, while eliminating donor-site morbidity associated with harvesting autologous bone graft. These impressively high fusion rates achieved with allograft in pediatric patients are similar to results reported in adults. While previous studies have suggested that such admirable fusion rates are related to improved internal fixation techniques, most patients also had their allograft fusions augmented with BMP. This review suggests that allograft fusion can produce high fusion rates in pediatric patients undergoing OCF or PCF with rigid internal fixation, but the importance of the role BMP plays in fusion is undetermined.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Tuite, Rodriguez, Carey. Acquisition of data: Tuite, Reintjes, Amankwah. Analysis and interpretation of data: Tuite, Reintjes, Amankwah. Drafting the article: Tuite, Reintjes, Amankwah. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Tuite. Statistical analysis: Amankwah. Study supervision: Tuite.

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