The clinical efficacy of hydroxyapatite and its composites in spinal reconstruction: a meta-analysis

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Abstract. – OBJECTIVE: Synthetic hydroxyapatite (HA) and its related materials have made great progress in basic research and clinical application in spinal repair and reconstruction. However, the effect of HA and its composites used in spinal fusion still remained controversial. This meta-analysis aimed at evaluating the efficacy and safety of HA compared with autologous bone.

MATERIALS AND METHODS: A systematic search in PubMed, MEDLINE, China National Knowledge Internet, EMBASE, and the Cochrane Library was conducted for relevant studies from inception until May 2021. Studies investigating the application of HA and its related composites in spinal fusion were selected for analysis.

RESULTS: The operation time of patients treated with artificial bone containing HA was less than that of patients with autologous bone ($p = 0.02$). The amount of operative blood loss in patients in the HA group was less than that in the autograft group ($p = 0.007$). Patients treated with autologous bone got a more significant advantage in fusion rate at 6 months ($p = 0.009$). Nevertheless, there was no significant difference in the fusion rate between patients in the two groups at 12 months or no less than 24 months postoperatively ($p = 0.24$; $p = 0.87$). Compared to the autograft group, the HA group significantly decreased postoperative adverse events ($p = 0.03$). Furthermore, there was no significant difference in the Oswestry Disability Index ($p = 1.00$) nor the Visual Analogue Scale score ($p = 0.94$) between the two groups.

CONCLUSIONS: This meta-analysis suggests that the clinical application of HA and its related composite materials in spinal reconstruction is comparable to that of autologous bone, with satisfactory efficacy and safety.

Key Words: Fusion, Hydroxyapatite, Bone graft, Meta-analysis.

Introduction

In spinal surgery, the graft materials for bone repair and reconstruction materials have been a major focus of research due to the need for a variety of conditions, such as trauma, tumor, infection, congenital and degenerative disease. Clinically, the autologous bone graft is considered the gold standard and the best biological graft material since it has a reliable fusion rate due to its excellent osteoconductivity and osteoinductive properties. However, there are also some complications, such as persistent pain, hematomas, wound infection, and changes in appearance at the donor site. In addition, allogeneic bone has been regarded as a suitable alternative for autogenous bone in orthopedic surgery. However, its use has been increasingly questioned because of the inferior fusion effect and the potential risk of disease transmission. Therefore, the clinical application of artificial bone substitutes and three-dimensional printing technology in orthopedic surgery has gained much attention. There are many kinds of artificial bone grafts with good biocompatibility, such as calcium phosphate cement, calcium sulfate, synthetic hydroxyapatite (HA), bioglass, and degradable polymer. However, because of the poor biological performance and mechanical properties of single-pattern artificial material, recent studies have focused on the combination of artificial bone with different bioactive substances, which can significantly increase the biological and mechanical properties of the bone graft. Furthermore, some researchers have used tissue engineering technology to inoculate seed cells on the skeleton of absorbable artificial bone materials to better reconstruct bone and cartilage tissue.
Among them, nano-hydroxyapatite (n-HA) and its composites, such as nano-hydroxyapatite/polyamide 66 (n-HA/PA66), have made great progress in basic research and clinical application in spinal repair and reconstruction.

Although HA and its related materials have been gradually applied in clinical work recently, there have been no systematic analyses on the clinical efficacy of these artificial bone grafts. Given this background, a meta-analysis was performed to compare the actual clinical application effect of HA and related composite materials with autologous bone in spinal reconstruction. We presented the following article in accordance with the PRISMA checklist.

**Materials and Methods**

**Search Strategy**

Two researchers independently searched the literature in PubMed, MEDLINE, China National Knowledge Internet (CNKI), EMBASE, and the Cochrane Library using the keywords “hydroxyapatite”, “bone graft”, “spine”, “fusion”, etc. Besides, the citation lists of retrieved articles were scanned to identify additional relevant studies. The retrieval time started from the establishment date of the database to May 2021. There were no restrictions on the language of the included studies.

**Inclusion Criteria and Exclusion Criteria**

Studies were considered eligible for this meta-analysis if they met the following criteria: (1) randomized controlled trials (RCTs) or cohort, cross-sectional and case-control studies; (2) patients must receive spinal fusion surgery; (3) completion of at least 6 months of follow-up; and (4) sufficient published data to estimate standardized mean difference (SMD), or odds ratio (OR) with a 95% confidence interval (CI).

The exclusion criteria were as follows: (1) case reports, letters, reviews, editorials, abstracts, or meeting proceedings; (2) studies without a clear description of the design; (3) studies lacking comparable results; and (4) repeated reports of previous studies.

**Study Selection, Data Extraction, and Quality Evaluation**

Two researchers jointly developed retrieval strategies and independently decided on the inclusion of the literature. Initial literature screening was performed by assessing the title and abstract of the study. After omitting the unrelated studies, further screening was conducted by reading the full text. The final included studies were determined in strict accordance with the inclusion criteria and exclusion criteria. Any disputes were resolved by a third researcher.

Then, two researchers independently extracted available data from included studies for analysis. The extracted data from all eligible studies covered characteristics of the study (author, publication year, study design, country of origin, and study period) and demographics of patients (sample size, mean age, gender ratio, operation type, and follow-up duration). Data of interest that could not be obtained directly from the texts would be recalculated. The aggregated data were validated by a third researcher.

The two researchers independently assessed the quality of the included study according to the Newcastle-Ottawa scale (NOS)\(^3\), which covered three aspects concerning object selection, comparability, and exposure. The maximum score was 9, and studies with a score ≥ 6 were considered high-quality. Disagreements were resolved through discussion.

**Statistical Analysis**

Statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Oxford, UK). ORs were used to calculate the results of dichotomous effect sizes and SMDs were used to calculate the results of continuous effect sizes. A 95% CI was determined for each effect size. The heterogeneity of each study was tested by Chi-squared tests and I-squared (I\(^2\)) statistics. When p-value was > 0.1 and I\(^2\) value was < 50%, there was no heterogeneity, and the fixed-effect model (FEM) was used for analysis. If statistical heterogeneity cannot be eliminated, the random-effect model (REM) was applied. Sensitivity analysis was performed by excluding individual studies and recalculating the effects.

**Results**

**Study Selection Process**

A total of 1,353 relevant articles were preliminarily obtained through the database search. After removing duplicate manuscripts, 382 studies remained. Of these, 237 were abandoned through title and abstract review. The full texts of the remaining 145 studies were examined for eligibility, and those were read in full text for further screening. However, 133 studies were excluded due to incomplete full texts, no outcomes of inter-
est, insufficient data, lacking comparable results, and repeated results. Ultimately, a total of 12 articles were selected in the final meta-analysis. The process of literature retrieval was shown in Figure 1.

**Basic Characteristics and Quality Assessment of Studies**

Among the 12 included articles, 8 were randomized controlled studies, 1 was a prospective non-randomized study, and 3 were retrospective studies (2 were cohort studies and 1 was a case-control study). The sample sizes ranged from 29 to 463 and together they presented a total of 1337 patients. Patients who underwent spinal surgery using artificial bone materials with HA were termed the HA group, while others who underwent the operation with autologous bone were assigned to the autograft group. For reporting clinical outcomes, six studies reported the operation time. Six studies recorded the amount of operative blood loss. Seven of them mentioned the postoperative adverse events. Two studies calculated the improvement rate of the Oswestry Disability Index (ODI) and four studies kept a re-
Application of hydroxyapatite materials in spine surgery

There were four separate studies reporting the fusion rate at 6, 18, 20, and 24 months (or more) \(^{15,17,20,24}\) respectively. Furthermore, methodological quality was assessed in accordance with the NOS and all included studies could be regarded as relatively high quality. More details of the basic characteristic were summarized in Table I.

**Results of Data Analysis**

**Operation time**

A total of six included studies \(^{14,16,19-21,24}\) containing 1008 patients examined the operation time in both groups. There was heterogeneity among the studies (Chi^2 = 28.68, \( p < 0.0001, I^2 = 79\%\)) and the REM was used for analysis (Figure 2). The operation time of HA patients was significantly less than the time observed in autologous patients (SMD = -0.40, 95% CI: -0.72 to -0.07, \( p = 0.02 \)).

**Operative blood loss**

Six studies \(^{13,16,19-21,24}\) consisting of 1008 patients documented operative blood loss. The REM was then employed because of high heterogeneity (Chi^2 = 60.13, \( p < 0.00001, I^2 = 90\%\)) (Figure 3). The amount of blood loss in HA patients was significantly less than that in autologous patients (SMD = -0.65, 95% CI: -1.12 to -0.18, \( p = 0.007 \)).

**Fusion rate**

The fusion rate at 6 months after operation was assessed in four studies \(^{18,20,22,25}\) including 451 patients. Low heterogeneity was observed across each study (Chi^2 = 3.30, \( p = 0.35, I^2 = 9\%\)), so the FEM was applied (Figure 4). The results showed that patients in autograft group received a significantly higher fusion rate at 6 months postoperatively (OR = 1.74, 95% CI: 1.15 to 2.62, \( p = 0.009 \)).

Data on fusion rate at 12 months after operation were available for analysis from four studies \(^{20,22,25}\) containing 826 patients. Because of low

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**Figure 2.** Forest plot of the operation time in HA group versus autograft group. HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

**Figure 3.** Forest plot of the operative blood loss in HA group versus autograft group. HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<td>22.7</td>
<td>51</td>
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<td>20</td>
<td>135</td>
<td>18</td>
<td>19</td>
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<td>19</td>
<td>20</td>
<td>146</td>
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<td>18</td>
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</table>

Total (95% CI) 503 505 100.0% 0.04 [-0.72, -0.07]
<table>
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<th>Author</th>
<th>Publication Year</th>
<th>Country</th>
<th>Study Period</th>
<th>Study Design</th>
<th>Sample Size (Case/Control)</th>
<th>Age (Years)</th>
<th>Sex (M:F)</th>
<th>Operation Type</th>
<th>Follow-up Time (Months)</th>
<th>NOS Score</th>
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<td>Delécrin et al14</td>
<td>2000</td>
<td>France</td>
<td>1989 - 1993</td>
<td>Randomized controlled study</td>
<td>58 (28/30)</td>
<td>18.2±2.6 (Case) 17.5±3.3 (Control)</td>
<td>NA</td>
<td>Posterior correction and spondylodesis</td>
<td>More than 24</td>
<td>8</td>
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<tr>
<td>McConnell et al15</td>
<td>2003</td>
<td>UK</td>
<td>NA</td>
<td>Randomized controlled study</td>
<td>47 (Case) 47 (Control)</td>
<td>9.4 (Case) 6:10 (Control)</td>
<td>NA</td>
<td>Anterior cervical decompression and fusion</td>
<td>24</td>
<td>8</td>
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<td>Korovessis et al16</td>
<td>2005</td>
<td>Greece</td>
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<td>Randomized controlled study</td>
<td>58±8 (Case) 61±11 (Control)</td>
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<td>48</td>
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<tr>
<td>Neen et al17</td>
<td>2006</td>
<td>UK</td>
<td>2000 - 2002</td>
<td>Prospective case-control study</td>
<td>100 (50/50)</td>
<td>49 (Case) 48 (Control)</td>
<td>25:25 (Case) 25:25 (Control)</td>
<td>Posterolateral lumbar fusion</td>
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<td>2004 - 2006</td>
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<td>NA</td>
<td>Anterior cervical decompression and fusion</td>
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<td>7</td>
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<td>Dawson et al19</td>
<td>2009</td>
<td>USA</td>
<td>2003 - 2004</td>
<td>Randomized controlled study</td>
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<td>10:15 (Case) 9:12 (Control)</td>
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<td>8</td>
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<tr>
<td>Dimar et al20</td>
<td>2009</td>
<td>USA</td>
<td>NA</td>
<td>Randomized controlled study</td>
<td>53.2 (Case) 52.3 (Control)</td>
<td>108:131 (Case) 95:129 (Control)</td>
<td>NA</td>
<td>Posterior lumbar decompression and intertransverse fusion</td>
<td>24</td>
<td>8</td>
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<tr>
<td>Deng et al21</td>
<td>2016</td>
<td>China</td>
<td>2010 - 2013</td>
<td>Retrospective case-control study</td>
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<td>Transforaminal lumbar interbody fusion</td>
<td>12</td>
<td>6</td>
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<tr>
<td>vonder- Hoeh et al22</td>
<td>2017</td>
<td>Germany</td>
<td>2010 - 2014</td>
<td>Randomized controlled study</td>
<td>64.9±8.4 (Case) 62.0±9.2 (Control)</td>
<td>20:22 (Case) 21:30 (Control)</td>
<td>NA</td>
<td>Transforaminal lumbar interbody fusion</td>
<td>12</td>
<td>8</td>
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<tr>
<td>Cho et al23</td>
<td>2017</td>
<td>South Korea</td>
<td>2013 - 2016</td>
<td>Randomized controlled study</td>
<td>52±7±10.4 (Case) 51.3±9.5 (Control)</td>
<td>25:22 (Case) 28:23 (Control)</td>
<td>NA</td>
<td>Posterior lumbar decompression and intertransverse fusion</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hu et al24</td>
<td>2019</td>
<td>China</td>
<td>2009 - 2011</td>
<td>Retrospective cohort study</td>
<td>60±12.5 (Case) 66.1±9.6 (Control)</td>
<td>6:14 (Case) 4:16 (Control)</td>
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<td>Anterior lumbar decompression and fusion</td>
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<td>Rickert et al25</td>
<td>2019</td>
<td>Germany</td>
<td>2012 - 2013</td>
<td>Randomized controlled study</td>
<td>60±12.5 (Case) 66.1±9.6 (Control)</td>
<td>6:14 (Case) 4:16 (Control)</td>
<td>NA</td>
<td>Anterior lumbar interbody fusion</td>
<td>12</td>
<td>8</td>
</tr>
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</table>

Table I. Basic characteristics of enrolled studies. NA, not available; M, male; F, female; NOS, Newcastle-Ottawa scale.
heterogeneity among included studies (Chi² = 1.93, \( p = 0.59, \Gamma = 0\% \)), the FEM was utilized (Figure 5). There were no significant differences in the fusion rate at 12 months post-operation between them (OR = 1.27, 95% CI: 0.85 to 1.91, \( p = 0.24 \)).

With respect to the fusion rate at 24 months (or more), four studies (15,17,20,24) consisting of 590 patients were pooled for this outcome by the REM due to high heterogeneity (Chi² = 6.64, \( p = 0.08, \Gamma = 55\% \)) (Figure 6). Again, the results exhibited no significant difference in the fusion rate between the two groups at 24 months (or more) postoperatively (OR = 1.10, 95% CI: 0.36 to 3.38, \( p = 0.87 \)).

**Adverse event**

Seven (14,15,18,20,22,23,25) out of twelve studies including 768 patients recorded the postoperative adverse event. Low heterogeneity was observed across each study (Chi² = 3.66, \( p = 0.61, \Gamma = 0\% \)), so the FEM was applied (Figure 7). It was indicated that the autograft group would increase the incidence of postoperative adverse events (OR = 0.59, 95% CI: 0.36 to 0.96, \( p = 0.03 \)).

**ODI**

As regards the ODI, 170 patients from two studies (16,23) were pooled in the analysis. There was low heterogeneity across each study (Chi² = 0.18, \( p = 0.91, \Gamma = 0\% \)) and we used the FEM (Figure 8). No significant difference was found between HA and autograft groups (SMD = 0.00, 95% CI: -0.30 to 0.30, \( p = 1.00 \)).

**VAS**

A total of 489 patients from four studies (16,21,22,24) reported the comparable VAS score. A FEM was adopted as the heterogeneity among included studies was relatively low (Chi² = 1.25, \( p = 0.87, \Gamma = 0\% \)) (Figure 9). As a result, it was not significantly different between the two groups (SMD = -0.01, 95% CI: -0.18 to 0.17, \( p = 0.94 \)).
Sensitivity Analysis

In the meta-analysis of the operation time, due to heterogeneity among the studies, each study was excluded until \( p > 0.1 \) and \( I^2 < 50\% \). The studies by Korovessis et al\(^{16}\), Deng et al\(^{21}\), and Hu et al\(^{24}\) were the sources of heterogeneity. However, the results did not change after excluding these studies.

There was also heterogeneity in the meta-analysis of the amount of operative blood loss, and each study was then excluded one by one. However, the source of heterogeneity could not be identified.

Regarding the analysis of fusion rate for 24 months (or more), the high heterogeneity was attributed to the included study by Dimar et al\(^{20}\). The \( I^2 \) value decreased from 55\% to 0\% after we excluded this study, and the results remained significantly different.

Discussion

As both a mineral and a biological material, HA is the main inorganic component of teeth and bones, accounting for 70-90\% of bone mass\(^{26}\). Since the 1980s, the material has been used as a bone graft in orthopedics, craniofacial surgery, and dentistry\(^{27}\). However, the application of HA is limited by its poor mechanical properties, including high brittleness and low flexural strength. With the development of bioengineering technology and material sciences, HA can be combined with a variety of other materials to greatly expand the application of it. Synthetic HA with stable chemical properties is similar to the inorganic components of the human body. Moreover, the excellent biocompatibility, osteoconduction, and osteoinduction of n-HA have also been widely confirmed in recent years\(^{28,29}\). It can be used
as the basic component in many different types of bone graft materials. At present, HA is mainly combined with the following materials: natural polymer materials (collagen, chitosan, dextran, silk fibroin, cellulose, etc.), synthetic polymer materials (polyamide, polylactic acid, polyetheretherketone, polyhydroxyglycolic acid, etc.), and bioactive factors. It also has been reported that HA can combine with insulin-like growth factor, bone marrow mesenchymal stem cells, antibiotics, and anti-tumor drugs to get the desired and specific function. Moreover, polyamide composites such as n-HA/PA66 have been widely used in clinical practice with good mechanical properties and biocompatibility. The compressive strength, bending strength, and elastic modulus of the composites are similar to those of human cortical bone by toughening n-HA with polyamide.

To the best of our knowledge, this is the first meta-analysis covering all relevant studies to compare the clinical and radiological outcomes between HA and autograft in spinal fusion. Patients in this analysis received spinal fusion including interbody fusion or intertransverse fusion. The age range of the patients in the including studies was large, but there was no significant difference in age between the two groups in each study. Likewise, no significant difference was found in gender among patients in the HA group and the autograft group. The operation time and operative blood loss are related to the intraoperative and postoperative safety of patients. It is well known that the longer the operation time, the higher the incidence of intraoperative complications such as infection and anesthetic accidents. Excessive intraoperative bleeding may cause hemorrhagic shock and organ damage, which can be life-threatening. The meta-analysis results of operation time and operative blood loss in the HA group were less than those in the autograft group, suggesting that spine surgery with HA and its related materials resulted in shorter operation time and less blood loss, which was much safer for patients undergoing surgery. We also attempted to evaluate the safety of treatment by assessing the incidence of perioperative adverse events. The results demonstrated that surgery using autologous bone grafts was associated with a greater risk of perioperative complications, which included hematoma, infection, and persistent pain at the donor site, as well as the bedridden-related complications. The iliac crest is the most common autologous bone graft because

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HA</th>
<th>Autograft</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
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<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
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<td>39.3</td>
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<tr>
<td>Korovessis et al. 2005 (2)</td>
<td>43</td>
<td>28</td>
<td>20</td>
<td>47</td>
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<tr>
<td>Total (95% CI)</td>
<td>82</td>
<td>88</td>
<td>100.0%</td>
<td>0.00 [0.30, 0.30]</td>
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</tbody>
</table>

Heterogeneity: Ch² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

Figure 8. Forest plot of the improvement of ODI in HA group versus autograft group. ODI, Oswestry Disability Index; HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HA</th>
<th>Autograft</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
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<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
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<td>0.87</td>
<td>124</td>
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<td>2.7</td>
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<td>254</td>
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<td>-0.011 [-0.18, 0.17]</td>
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Heterogeneity: Ch² = 1.25, df = 4 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

Figure 9. Forest plot of the improvement of VAS in HA group versus autograft group. VAS, Visual Analogue Scale; HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.
it contains a large amount of cortical and cancellous bone, where the area is rich in blood supply and growth factors that promote osteogenesis. However, the addition of surgical areas inevitably results in an increased incidence of adverse events in this region and prolonged postoperative bed time. In this meta-analysis, we grouped and counted the postoperative fusion rate at three different time points. Then, we draw a conclusion that patients undergoing spinal fusion with autografts received a higher fusion rate compared with the HA and related materials at 6 months postoperatively. Nevertheless, there was no significant difference in the fusion rate between patients in the two groups at 12 and 24 months (or more). This suggested that autologous bone graft rich in osteoblasts and growth factors was conducive to rapid repair and reconstruction of bone tissue in the early stage. From a long-term perspective, the two materials had similar effects on spinal fusion. In addition, no statistical differences were found concerning the improvement degree of postoperative ODI and VAS scores between the HA group and the autograft group. The results of this study suggested that the HA and its related materials had a similar effect to autograft in spinal fusion, with shorter operation time, less blood loss, and lower incidence of adverse events, which indicated that this kind of artificial biomaterial was safe and effective.

In this meta-analysis, there was heterogeneity in the research of operation time between the HA group and the autograft group. Studies by Korovessis et al., Deng et al., and Hu et al. were found to be the sources of heterogeneity, and the results did not change after excluding each study. In the analysis of operative blood loss between the two groups, there was heterogeneity among the studies and each study was excluded one by one. Unfortunately, we did not detect which study should be responsible for the high heterogeneity. Perhaps the data mentioned in the article was not related to heterogeneity, so we might not find the source of it. As regards the analysis of fusion rate at 24 months (or more), the high heterogeneity was attributed to the included study by Dimar et al. A large number of patients in this research were lost to follow-up (45 in the HA group and 55 in the autograft group) at the time point of 24 months, which may have been the cause of the heterogeneity. The results remained significantly different after we excluded this study. In the above-mentioned meta-analyses, we used the REM, and the results were deemed to be reliable.

**Limitations**

Several limitations should not be ignored in this study. First, not all studies selected were RCTs, so there might be some bias in the results due to the design of observational study. Second, the results might have been influenced by the included patients with different diagnoses and spinal segments. Third, the evaluation of spinal fusion in the included studies relied primarily on radiological assessment. However, it was reported that the predictive value of assessment by radiological methods was less than 70%. Some novel assessment methods are required to provide more accurate results for determining spinal fusion. Furthermore, due to the small sample size, there was no subgroup analysis for different types of HA-derived complexes, which could lead to certain risk biases. Therefore, increasing the sample size is warranted to more accurately verify and confirm the efficacy of HA and its related composites in spinal reconstruction.

**Conclusions**

This meta-analysis was conducted to examine the clinical efficacy and safety of HA and related materials compared with autologous bone in spinal reconstruction. Patients using autologous bone grafts could get a higher fusion rate than those with HA materials in the early prognosis. However, from a long-term perspective, the two materials had similar effects on spinal fusion. Besides this, patients who received spinal reconstruction with HA materials could get shorter operation time, less operative blood loss, and fewer postoperative adverse events than autograft ones. The two different bone grafts had little difference in the improvement of postoperative ODI and VAS scores. Therefore, the application of HA and its related composite materials in spinal fusion is comparable to that of autologous bone, with satisfactory clinical efficacy and reliable safety. More RCTs with larger sample sizes should be encouraged to further validate the effectiveness of HA-related materials in spinal reconstruction.

**Conflicts of Interest**

The authors declare that they have no conflict of interest.

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**Ethical Statement**
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