European Review for Medical and Pharmacological Sciences 2022; 26: 4614-4624

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

X.-J. LIU[1,2], Q.-S. ZHU[1], H.-F. SUN[3], X.-J. SONG[1], C.-L. WANG[1], Y.-T. WU[1], Y.-H. MA[1]

[1]Department of Spine Surgery, China-Japan Union Hospital of Jilin University, Changchun, China
[2]Department of Orthopedics, Second Affiliated Hospital & Institute of Cancer Stem Cell, Dalian Medical University, Dalian, China
[3]Department of Respiratory Medicine, Chinese People's Liberation Army No. 964 Hospital, Changchun, China

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[1] due to its excellent osteoconductive and osteoinductive properties. However, there are also some complications, such as persistent pain, hematomas, wound infection, and changes in appearance at the donor site[2-4]. 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[5]. Therefore, the clinical application of artificial bone substitutes and three-dimensional printing technology in orthopedic surgery has gained much attention[6,7]. 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[8-10] 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[11,12].

Corresponding Author: Yihang Ma, MD; e-mail: myx18@mails.jlu.edu.cn

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)[13], 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-

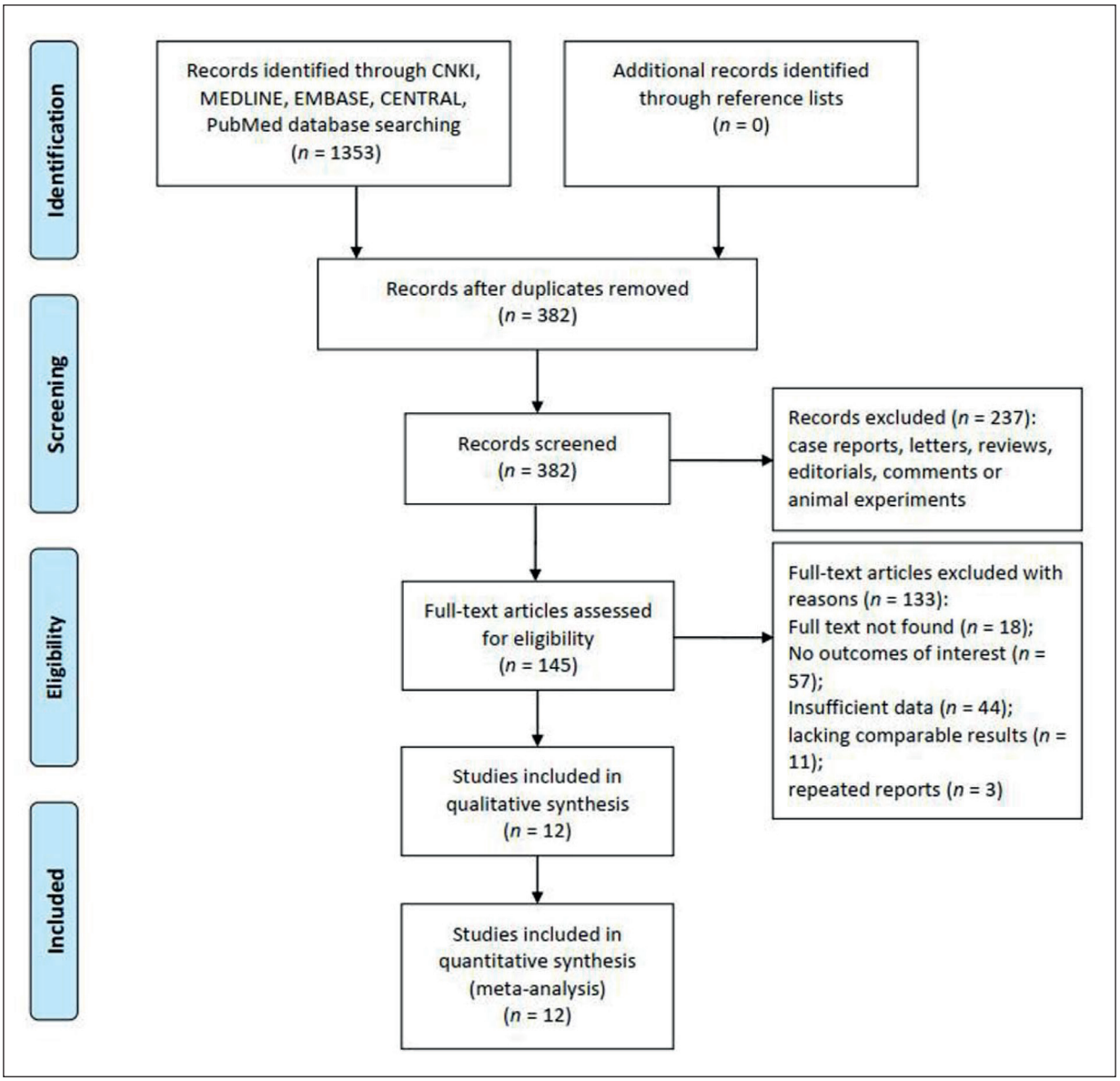

Figure 1. PRISMA flowchart of the study selection.

est, insufficient data, lacking comparable results, and repeated results. Ultimately, a total of 12 articles[14-25] 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[14-16,19,20,22,23,25], 1 was a prospective non-randomized study[17], and 3 were retrospective studies (2 were cohort studies[18,24] and 1 was a case-control study[21]). 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[14,16,19-21,24] reported the operation time. Six studies[14,16,19-21,24] recorded the amount of operative blood loss. Seven[14,15,18,20,22,23,25] of them mentioned the postoperative adverse events. Two studies[16,23] calculated the improvement rate of the Oswestry Disability Index (ODI) and four studies[16,21,22,24] kept a re-

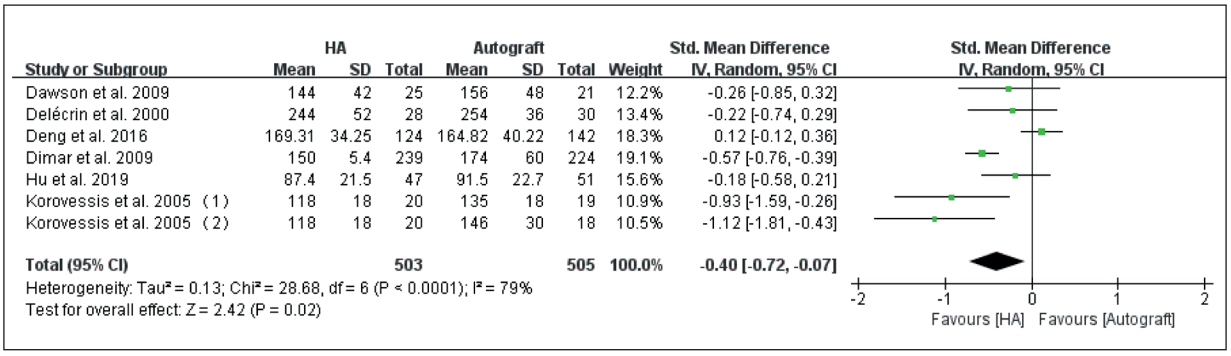

Figure 2. Forest plot of the operation time in HA group versus autograft group. HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

cord of the Visual Analogue Scale (VAS) score. There were four separate studies reporting the fusion rate at 6[18,20,22,25], 12[20-22,25], 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[14,16,19-21,24] 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

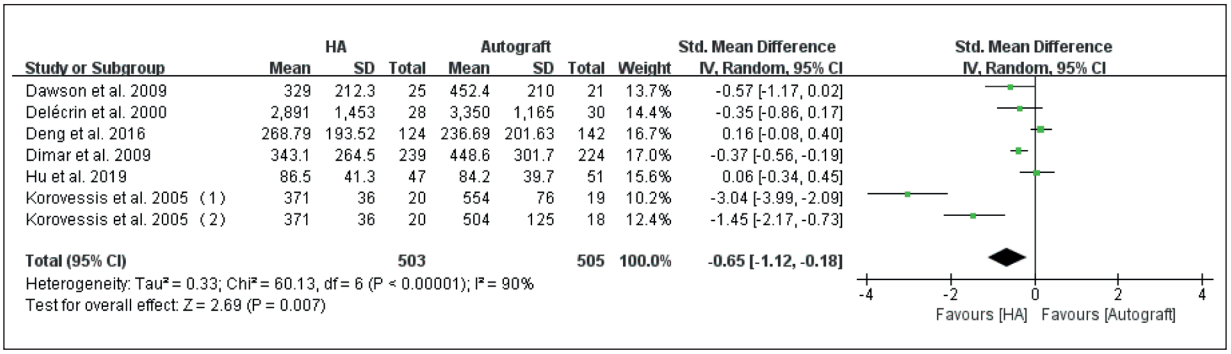

Figure 3. Forest plot of the operative blood loss in HA group versus autograft group. HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

Table I. Basic characteristics of enrolled studies. NA, not available; M, male; F, female; NOS, Newcastle-Ottawa scale.

Author	Publication Year	Country	Study Period	Study Design	Sample Size (Case/Control)	Age (Years)	Sex (M:F)	Operation Type	Follow-up Time (Months)	NOS Score
Delécrin et al[14]	2000	France	1989 - 1993	Randomized controlled study	58 (28/30)	18.2±2.6(Case) 17.5±3.3 (Control)	NA	Posterior correction and spondylodesis	More than 24	8
McConnell et al[15]	2003	UK	NA	Randomized controlled study	29 (13/16)	47 (Case) 47 (Control)	9:4 (Case) 6:10 (Control)	Anterior cervical decompression and fusion	24	8
Korovessis et al[16]	2005	Greece	NA	Randomized controlled study	39 (20/19)	58±8 (Case) 61±11(Control)	NA	Posterior lumbar decompression and intertransverse fusion	48	8
Neen et al[17]	2006	UK	2000 - 2002	Prospective case-control study	100 (50/50)	49 (Case) 48 (Control)	25:25 (Case) 25:25 (Control)	Posterolateral lumbar fusion	24	7
Chang et al[18]	2009	Taiwan, China	2004 - 2006	Retrospective cohort study	45 (22/23)	58.5±2.91 (Case) 51.39±2.27 (Control)	12:10 (Case) 14:9 (Control)	Anterior cervical decompression and fusion	More than 6	7
Dawson et al[19]	2009	USA	2003 - 2004	Randomized controlled study	46 (25/21)	55.9 (Case) 56.9 (Control)	10:15 (Case) 9:12 (Control)	Posterior lumbar decompression and intertransverse fusion	24	8
Dimar et al[20]	2009	USA	NA	Randomized controlled study	463 (239/224)	53.2 (Case) 52.3 (Control)	108:131 (Case) 95:129 (Control)	Posterior lumbar decompression and intertransverse fusion	24	8
Deng et al[21]	2016	China	2010 - 2013	Retrospective case-control study	266 (124/142)	53.28±12.51 (Case) 53.65±14.43 (Control)	61:63 (Case) 60:82 (Control)	Transforaminal lumbar interbody fusion	12	6
vonder-Hoeh et al[22]	2017	Germany	2010 - 2014	Randomized controlled study	48 (24/24)	64.3±12.6 (Case) 65.6±14.4 (Control)	7:17 (Case) 5:19 (Control)	Transforaminal lumbar interbody fusion	12	8
Cho et al[23]	2017	South Korea	2013 - 2016	Randomized controlled study	93 (42/51)	64.9±8.4 (Case) 62.0±9.2 (Control)	20:22 (Case) 21:30 (Control)	Posterior lumbar decompression and intertransverse fusion	6	8
Hu et al[24]	2019	China	2009 - 2011	Retrospective cohort study	98 (47/51)	52.5±10.4 (Case) 51.3±9.5 (Control)	25:22 (Case) 28:23 (Control)	Anterior cervical decompression and fusion	More than 84	7
Rickert et al[25]	2019	Germany	2012 - 2013	Randomized controlled study	40 (20/20)	60.6±12.5 (Case) 66.1±9.6 (Control)	6:14 (Case) 4:16 (Control)	Anterior lumbar interbody fusion	12	8

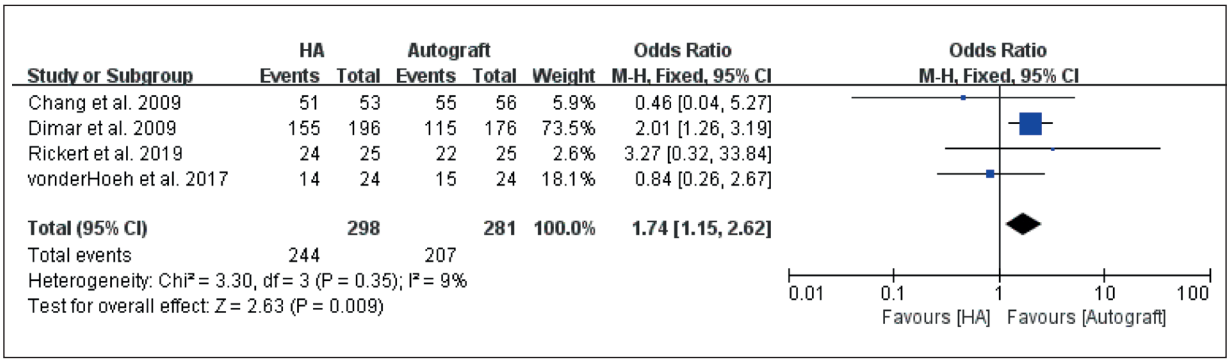

Figure 4. Forest plot of the fusion rate in HA group versus autograft group at 6 months post-operation. HA, hydroxyapatite; OR, odds ratio; CI, confidence interval.

heterogeneity among included studies (Chi^2 = 1.93, p = 0.59, I^2 = 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 (Chi^2 = 6.64, p = 0.08, I^2 = 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 (Chi^2 = 3.66, p = 0.61, I^2 = 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 (Chi^2 = 0.18, p = 0.91, I^2 = 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 (Chi^2 = 1.25, p = 0.87, I^2 = 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).

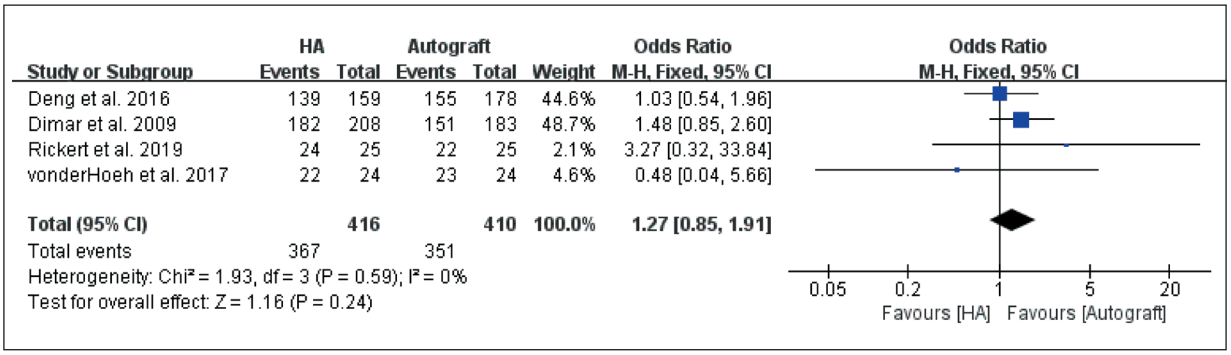

Figure 5. Forest plot of the fusion rate in HA group versus autograft group at 12 months post-operation. HA, hydroxyapatite; OR, odds ratio; CI, confidence interval.

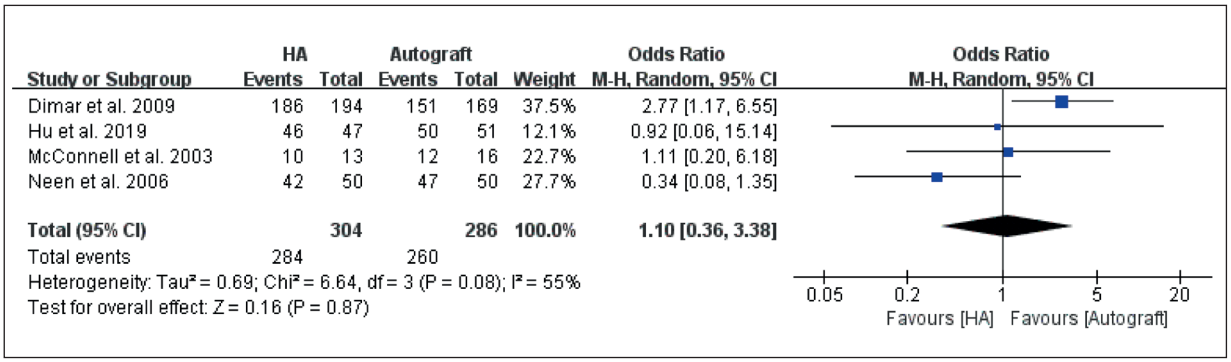

Figure 6. Forest plot of the fusion rate in HA group versus autograft group at 24 months (or more) post-operation. HA, hydroxyapatite; OR, odds ratio; CI, confidence interval.

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 expands 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

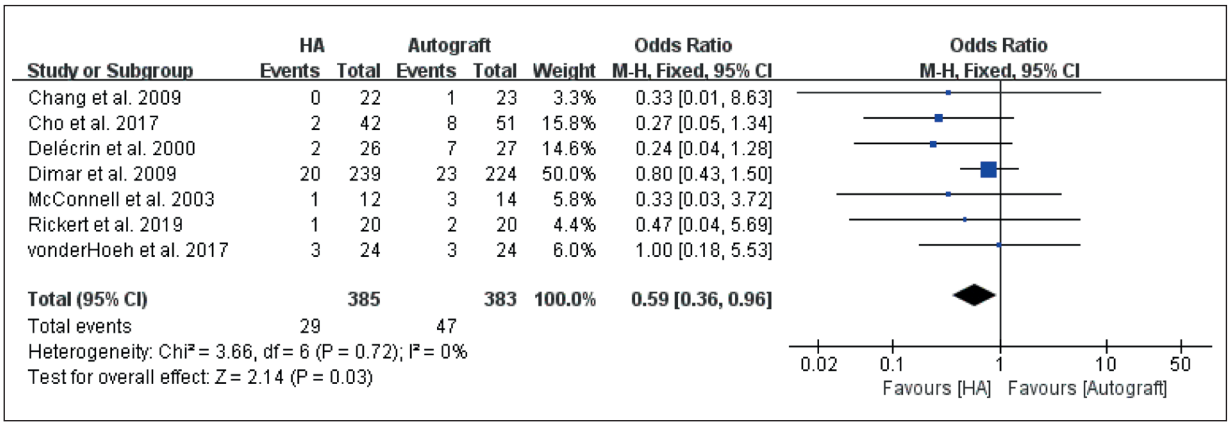

Figure 7. Forest plot of the postoperative adverse event in HA group versus autograft group. HA, hydroxyapatite; OR, odds ratio; CI, confidence interval.

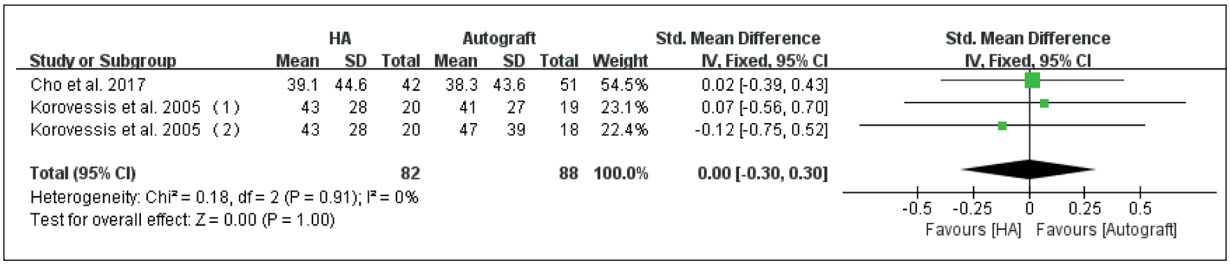

Figure 8. Forest plot of the improvement of ODI in HA group versus autograft group. ODI, Oswestry Disability Index; HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

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, polyethylene, 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[30,31]. Moreover, polyamide composites such as n-HA/PA66 have been widely used in clinical practice with good mechanical properties and biocompatibility[32,33]. 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[34], 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

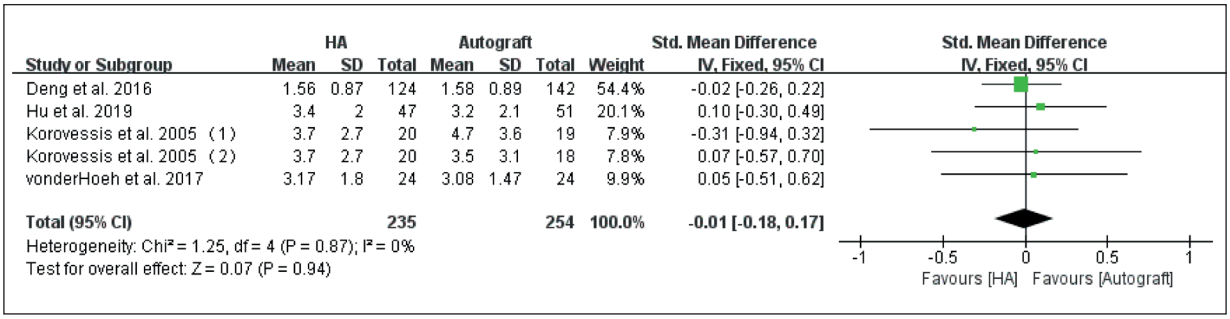

Figure 9. Forest plot of the improvement of VAS in HA group versus autograft group. VAS, Visual Analogue Scale; HA, hydroxyapatite; SMD, standardized mean difference; CI, confidence interval.

it contains a large amount of cortical and cancellous bone, where the area is rich in blood supply and growth factors that promote osteogenesis[35]. However, the addition of surgical areas inevitably results in an increased incidence of adverse events in this region and prolonged postoperative bedtime. 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[16], Deng et al[21], and Hu et al[24] 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[20]. 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%[36]. 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.

Acknowledgments

Y.-H. Ma would like to thank the care, support, and encouragement from Y.-Q. Zhang for this period.

Funding

None.

Authors' Contributions

(I) Conception and design: Y.-T. Wu, Q.-S. Zhu, X.-J. Liu, and C.-L. Wang; (II) Acquisition of data: Y.-H. Ma and X.-J. Liu; (III) Data analysis and interpretation: Y.-H. Ma, X.-J. Liu, and H.-F. Sun; (IV) Manuscript drafting: Y.-H. Ma and H.-F. Sun; (V) Revision making: X.-J. Song and C.-L. Wang; (VI) Supervision: Q.-S. Zhu and Y.-T. Wu; (VII) Final approval of manuscript: All authors.

Ethical Statement

Not applicable.

References

1) Ferrete-Barroso AM, González-Díaz R, Losada-Viñas JI. Anterior cervical arthrodesis using a vertebral body autograft. Rev Esp Cir Ortop Traumatol 2015; 59: 172-178.
2) Kinaci A, Neuhaus V, Ring DC. Trends in bone graft use in the United States. Orthopedics 2014; 37: e783-788.
3) Shibuya N, Jupiter DC. Bone graft substitute: allograft and xenograft. Clin Podiatr Med Surg 2015; 32: 21-34.
4) Putzier M, Strube P, Funk JF, Gross C, Mönig HJ, Perka C, Pruss A. Allogenic versus autologous cancellous bone in lumbar segmental spondylodesis: a randomized prospective study. Eur Spine J 2009; 18: 687-695.
5) Singh R, Singh D, Singh A. Radiation sterilization of tissue allografts: A review. World J Radiol 2016; 8: 355-369.
6) Komlev VS, Popov VK, Mironov AV, Fedotov AY, Teterina AY, Smirnov IV, Bozo IY, Rybko VA, Deev RV. 3D Printing of Octacalcium Phosphate Bone Substitutes. Front Bioeng Biotechnol 2015; 3: 81.
7) Xu N, Ye X, Wei D, Zhong J, Chen Y, Xu G, He D. 3D artificial bones for bone repair prepared by computed tomography-guided fused deposition modeling for bone repair. ACS Appl Mater Interfaces 2014; 6: 14952-14963.
8) Coughlan M, Davies M, Mostert AK, Nanda D, Willems PC, Rosenberg G, Ferch R. A Prospective, Randomized, Multicenter Study Comparing Silicated Calcium Phosphate versus BMP-2 Synthetic Bone Graft in Posterolateral Instrumented Lumbar Fusion for Degenerative Spinal Disorders. Spine (Phila Pa 1976) 2018; 43: E860-e868.
9) Hansraj KK. Stem Cells in Spine Surgery. Surg Technol Int 2016; 29: 348-358.
10) Lee GH, Makkar P, Paul K, Lee B. Incorporation of BMP-2 loaded collagen conjugated BCP granules in calcium phosphate cement based injectable bone substitutes for improved bone regeneration. Mater Sci Eng C Mater Biol Appl 2017; 77: 713-724.
11) Li L, Li J, Zou Q, Zuo Y, Cai B, Li Y. Enhanced bone tissue regeneration of a biomimetic cellular scaffold with co-cultured MSCs-derived osteogenic and angiogenic cells. Cell Prolif 2019; 52: e12658.
12) Diomede F, Gugliandolo A, Cardelli P, Merciaro I, Ettorre V, Traini T, Bedini R, Scionti D, Bramanti A, Nanci A, Caputi S, Fontana A, Mazzon E, Trubiani O. Three-dimensional printed PLA scaffold and human gingival stem cell-derived extracellular vesicles: a new tool for bone defect repair. Stem Cell Res Ther 2018; 9: 104.
13) Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.
14) Delécrin J, Takahashi S, Gouin F, Passuti N. A synthetic porous ceramic as a bone graft substitute in the surgical management of scoliosis: a prospective, randomized study. Spine (Phila Pa 1976) 2000; 25: 563-569.
15) McConnell JR, Freeman BJ, Debnath UK, Grevitt MP, Prince HG, Webb JK. A prospective randomized comparison of coralline hydroxyapatite with autograft in cervical interbody fusion. Spine (Phila Pa 1976) 2003; 28: 317-323.
16) Korovessis P, Koureas G, Zacharatos S, Papazisis Z, Lambiris E. Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. Eur Spine J 2005; 14: 630-638.
17) Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N. Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. Spine (Phila Pa 1976) 2006; 31: E636-640.
18) Chang WC, Tsou HK, Chen WS, Chen CC, Shen CC. Preliminary comparison of radiolucent cages containing either autogenous cancellous bone or hydroxyapatite graft in multilevel cervical fusion. J Clin Neurosci 2009; 16: 793-796.
19) Dawson E, Bae HW, Burkus JK, Stambough JL, Glassman SD. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. J Bone Joint Surg Am 2009; 91: 1604-1613.
20) Dimar JR, 2nd, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. J Bone Joint Surg Am 2009; 91: 1377-1386.
21) Deng QX, Ou YS, Zhu Y, Zhao ZH, Liu B, Huang Q, Du X, Jiang DM. Clinical outcomes of two types of cages used in transforaminal lumbar interbody

fusion for the treatment of degenerative lumbar diseases: n-HA/PA66 cages versus PEEK cages. J Mater Sci Mater Med 2016; 27: 102.

22) vonderHoeh NH, Voelker A, Heyde CE. Results of lumbar spondylodeses using different bone grafting materials after transforaminal lumbar interbody fusion (TLIF). Eur Spine J 2017; 26: 2835-2842.

23) Cho JH, Lee JH, Yeom JS, Chang BS, Yang JJ, Koo KH, Hwang CJ, Lee KB, Kim HJ, Lee CK, Kim H, Suk KS, Nam WD, Han J. Efficacy of Escherichia coli-derived recombinant human bone morphogenetic protein-2 in posterolateral lumbar fusion: an open, active-controlled, randomized, multicenter trial. Spine J 2017; 17: 1866-1874.

24) Hu B, Yang X, Hu Y, Lyu Q, Liu L, Zhu C, Zhou C, Song Y. The n-HA/PA66 Cage Versus the PEEK Cage in Anterior Cervical Fusion with Single-Level Discectomy During 7 Years of Follow-Up. World Neurosurg 2019; 123: e678-e684.

25) Rickert M, Fleege C, Papachristos I, Makowski MR, Rauschmann M, Arabmotlagh M. Clinical Outcome After Anterior Lumbar Interbody Fusion With a New Osteoinductive Bone Substitute Material: A Randomized Clinical Pilot Study. Clin Spine Surg 2019; 32: e319-e325.

26) Li J, Liu M, Qiu Y, Gan Y, Jiang H, Liu B, Wei H, Ma N. Urchin-like Hydroxyapatite/Graphene Hollow Microspheres as pH-Responsive Bone Drug Carriers. Langmuir 2021; 37: 4137-4146.

27) Harms C, Helms K, Taschner T, Stratos I, Ignatius A, Gerber T, Lenz S, Rammelt S, Vollmar B, Mittlmeier T. Osteogenic capacity of nanocrystalline bone cement in a weight-bearing defect at the ovine tibial metaphysis. Int J Nanomedicine 2012; 7: 2883-2889.

28) Bròdano GB, Giavaresi G, Lolli F, Salamanna F, Parrilli A, Martini L, Griffoni C, Greggi T, Arcangeli E, Pressato D, Boriani S, Fini M. Hydroxyapatite-Based Biomaterials Versus Autologous Bone Graft in Spinal Fusion: An In Vivo Animal Study. Spine (Phila Pa 1976) 2014; 39: e661-e668.

29) Rajula MPB, Narayanan V, Venkatasubbu GD, Mani RC, Sujana A. Nano-hydroxyapatite: A Driving Force for Bone Tissue Engineering. J Pharm Bioallied Sci 2021; 13: S11-s14.

30) Venkatesan J, Kim SK. Nano-hydroxyapatite composite biomaterials for bone tissue engineering--a review. J Biomed Nanotechnol 2014; 10: 3124-3140.

31) Ji Y, Wang M, Liu W, Chen C, Cui W, Sun T, Feng Q, Guo X. Chitosan/nHAC/PLGA microsphere vehicle for sustained release of rhBMP-2 and its derived synthetic oligopeptide for bone regeneration. J Biomed Mater Res A 2017; 105: 1593-1606.

32) Zhao Z, Guo L, Zhu Y, Luo W, Ou Y, Quan Z, Jiang D. Clinical Use of a New Nano-Hydroxyapatite/Polyamide66 Composite Artificial Lamina in Spinal Decompression Surgery: More Than 4 Years' Follow-Up. Med Sci Monit 2018; 24: 5573-5579.

33) Xiong Y, Ren C, Zhang B, Yang H, Lang Y, Min L, Zhang W, Pei F, Yan Y, Li H, Mo A, Tu C, Duan H. Analyzing the behavior of a porous nano-hydroxyapatite/polyamide 66 (n-HA/PA66) composite for healing of bone defects. Int J Nanomedicine 2014; 9: 485-494.

34) Marquis ME, Lord E, Bergeron E, Drevelle O, Park H, Cabana F, Senta H, Faucheux N. Bone cells-biomaterials interactions. Front Biosci (Landmark Ed) 2009; 14: 1023-1067.

35) Mahato NK. Characterization of cortico-cancellous bone along the iliac crest: focus on graft harvesting. Surg Radiol Anat 2011; 33: 433-437.

36) Brodsky AE, Kovalsky ES, Khalil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. Spine (Phila Pa 1976) 1991; 16: S261-265.