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The efficacy and safety of different anti-osteoporotic drugs for the spinal fusion surgery: A network meta-analysis

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Abstract

BACKGROUND

Administering anti-osteoporotic agents to patients perioperatively is a widely accepted approach for improving bone fusion rates and reducing the risk of complications. The best anti-osteoporotic agents for spinal fusion surgery remain unclear.

AIM

The purpose of this study was to investigate the efficacy and safety of different anti-osteoporotic agents in spinal fusion surgery *via* network meta-analysis.

METHODS

Searches were conducted in four electronic databases (PubMed, EMBASE, Web of Science, the Cochrane Library and China National Knowledge Infrastructure (CNKI)) from inception to November 2022. Any studies that compared anti-osteoporotic agents *vs* placebo for spinal fusion surgery were included in this network meta-analysis. Outcomes included fusion rate, Oswestry disability index (ODI), and adverse events. Network meta-analysis was performed by R software with the gemtc package.

RESULTS

In total, 13 RCTs were included in this network meta-analysis. Only teriparatide (OR 3.2, 95% CrI 1.4, 7.8) was more effective than placebo in increasing the fusion rate. The surface under the cumulative ranking curve (SUCRA) of teriparatide combined with denosumab was the highest (SUCRA, 90.9%), followed by teriparatide (SUCRA, 74.0%), zoledronic acid (SUCRA, 43.7%), alendronate (SUCRA, 41.1%) and risedronate (SUCRA, 35.0%). Teriparatide (MD -15, 95% CrI -28, -2.7) and teriparatide combined with denosumab (MD -20, 95% CrI -40, -0.43) were more effective than placebo in decreasing the ODI. The SUCRA of teriparatide combined with denosumab was highest (SUCRA, 90.8%), followed by teriparatide (SUCRA, 74.5%), alendronate (SURCA, 52.7), risedronate (SURCA, 52.1%), zoledronic acid (SURCA, 24.2%) and placebo (SURCA, 5.6%) for ODI. The adverse events were not different between groups.

CONCLUSION

This network meta-analysis suggests that teriparatide combined with denosumab and teriparatide alone significantly increase the fusion rate and decrease the ODI without increasing adverse events. Based on current evidence, teriparatide combined with denosumab or teriparatide alone is recommended to increase the fusion rate and to reduce ODI in spinal fusion patients.

INTRODUCTION

Low back pain (LBP) is one of the most frequent symptoms for which patients visit physicians around the world[1,2]. One frequently employed method for addressing degenerative lumbar conditions such as deformity, instability, lumbar stenosis, degenerative spondylolisthesis, and spinal trauma is spinal fusion surgery[3,4]. Pedicle screws, which are used to stabilize spinal instrumentation, are chosen according to their pullout strength and the bone mineral density in the spine[5,6]. Spinal fusion surgery is common in geriatrics, especially in aged women[7]. In general, spinal fusion patients are more likely to have low bone mass and osteoporosis[8,9]. Complications that have been reported in the surgical treatment of an osteoporotic spine using instrumentation

include spinal instability, implant migration leading to pseudarthrosis, instrumentation failure, and other related issues[10,11].

The incidence of pseudoarthrosis following lumbar spine fusion can range from 5% to 35% and is notably higher in individuals who have undergone fusion across three or more spinal levels[12]. Pseudarthrosis may result in spine pain and poor functional outcomes after spinal fusion surgery[13]. Therefore, choosing anti-osteoporotic drugs to increase the fusion rate after spinal surgery is an important challenge for spinal surgeons.

Anti-osteoporosis drugs, including antiresorptive or anabolic drugs, as well as drugs with a mixed mechanism of action, are well accepted to increase the fusion rate[14,15]. Among many anti-osteoporotic medicines, teriparatide, bisphosphonate and denosumab are most commonly used in clinical practice. Teriparatide, the synthetic form of human parathyroid hormone (PTH) 1-34, is used to treat postmenopausal osteoporosis[10,16-19]. Teriparatide has an anabolic effect on osteoblasts, not only increasing bone mineral density (BMD) and bone mass but also improving the microarchitecture of the skeleton[20]. Bisphosphonates are stable derivatives of inorganic pyrophosphate and potent antiresorptive agents[21]. The main bisphosphonates are alendronate, risedronate, ibandronate and zoledronic acid[22]. Bisphosphonates promote the apoptosis of osteoclasts, inhibit bone loss and increase bone density around the spine[23]. Although many studies have investigated the role of bisphosphonate administration after spinal fusion, the conclusions are still controversial. Denosumab is a fully human monoclonal antibody that binds RANKL, thereby blocking its interaction with RANK. Denosumab selectively inhibits osteoclastogenesis and has been approved by the U.S. Food and Drug Administration (FDA). Denosumab is well tolerated by patients, and it affects renal function less than other drugs[24].

While anti-osteoporotic medications have been recognized as effective for preventing bone loss during spinal fusion surgery, the most effective treatment regimen remains uncertain[25]. By utilizing Bayesian network meta-analysis, we indirectly compared therapies in cases where direct comparisons were not available, allowing for

a more precise assessment of efficacy by combining both direct and indirect comparisons.

This study aimed to determine the effectiveness and safety of various anti-osteoporotic medications in the context of spinal surgery using network meta-analysis.

MATERIALS AND METHODS

This network meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. This study was registered through PROSPERO (PROSPERO Registration number: CRD42023445654).

2.1 Search strategy

Two independent reviewers (Xiaoyuan He and Zhirong Zhao) performed searches in four electronic databases (PubMed, EMBASE, Web of Science, the Cochrane Library and China National Knowledge Infrastructure (CNKI)) from inception to November 2022. Moreover, we manually searched related references to retrieve eligible studies. The search terms used were: “Alendronate”, “Clodronic Acid”, “Etidronic Acid”, “Ibandronic Acid”, “Pamidronate”, “Risedronic Acid”, “Technetium Tc 99m Medronate”, “Zoledronic Acid”, “"Diphosphonates"[Mesh]” OR ‘‘bisphosphonate” OR “” “Parathyroid Hormone”, “Teriparatide” AND “Spinal Fusion’’. More detailed information regarding the search strategy can be found in **Supplement S1**. Ethical approval was not required for this systematic review and network meta-analysis since no patient contact took place.

2.2 Study eligibility criteria and exclusion criteria

Studies were included in this review if they met all the following population/intervention/comparison/outcome (PICOS) criteria: (P) the study recruited patients undergoing spinal fusion; (I) it tested anti-osteoporosis medicine(s) (bisphosphonates, teriparatide, or denosumab); (C) it compared the drug(s) to a placebo; (O) its outcomes were fusion rate, Oswestry disability index (ODI) and/or adverse events; and (S) the study was a randomized controlled trial (RCT). The primary outcome of this meta-analysis was the fusion rate, which is predominantly influenced in

the positive direction by the increase in bone mineral density induced by these anti-osteoporotic drugs. The secondary outcomes were the Oswestry disability index (ODI) and adverse events. The inclusion of ODI in our analysis helped evaluate dysfunction related to back pain. The study encompassed parallel-group randomized controlled trials, as well as first-phase crossover trials and multiarm trials. The exclusion criteria were as follows: (1) case reports and comments; (2) studies with insufficient data; (3) reviews or meta-analyses; (4) studies with only case groups; and (5) no follow-up after discharge.

2.3 Assessment of risk of bias

The revised Cochrane risk-of-bias tool for randomized trials was employed[26]. Risk of bias from five different domains was assessed: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcome and (5) selection of the reported result. Risk of bias is reported as 'low risk of bias,' 'some concerns' or 'high risk of bias'. There are specific and clear instructions in this tool to help reviewers assess the risk of bias as "high", "low", or "unclear". Divergences were resolved by face-to-face discussion, or in case of persistent disagreement, a third experienced author was consulted.

2.4 Data extraction

Two authors (Huanxiong Chen and Zhirong Zhao) independently extracted all relevant general information from eligible studies using a standardized form in Microsoft Excel (Microsoft Excel for Windows 2011, Version 14.4.9, 2010; Microsoft Corp, Redmond, Wash). General characteristics of the studies included first author, publication year, location, surgical indication, numbers in the comparator groups and control, mean ages of the comparator and control groups, sex ratio, follow-up duration, dose of drugs and outcomes of interest (fusion rate, ODI and adverse events). To mitigate the effects of withdrawal bias, we prioritized the use of intention-to-treat analysis data whenever possible. In cases where outcome data were ambiguous, we reached out to the corresponding author *via* email in an effort to obtain the necessary information.

2.5 Statistical analysis

Network meta-analysis concerning the effects of the anti-osteoporosis drugs on fusion rate was performed by a random-effect model within a Bayesian framework, using packages "gemtc" and "rjags" of R software (version 3.5.1, https://www.r-project.org/). We ran the Markov chain Monte Carlo (MCMC) simulation with four chains for each model, using 500,000 iterations, a burn-in of 20,000 iterations and extraction of every 10th value (Sutton and Abrams[27]). Using the median values from the posterior distribution, we calculated the estimated outcomes (measured as mean differences or odds ratios) along with their corresponding 95% confidence intervals. If the 95% confidence intervals for the odds ratios did not encompass 1 or for the mean differences did not encompass 0, this indicated a statistically significant difference. A P value less than 0.05 was defined as statistically significant. The surface under the cumulative ranking curve (SUCRA) values were also calculated to rank different interventions. The larger the value of SURCA, the better the effect of the intervention. Heterogeneity was evaluated using the I^2 test, and thresholds were defined as 50% when I^2 was less than 50%, which indicated low heterogeneity. The global inconsistency was evaluated by comparing the fit of consistency and inconsistency models using the deviance information criterion (DIC), where a similar DIC of different models indicates good consistency. We utilized node-splitting analysis to evaluate local inconsistency, whereby a P value greater than 0.05 indicated that there was no significant inconsistency between the direct pairwise results and the indirect results.

RESULTS

3.1 Search results

The initial search of four databases (PubMed, EMBASE, Web of Science, the Cochrane Library and CNKI) yielded 732 articles, 173 of which were excluded as duplicates. After reading the title and abstract, 542 articles were filtered out based on our inclusion and exclusion criteria. After reading the full texts manually, 5 articles

were excluded for various reasons. In the end, 13 studies were included in this network meta-analysis (**Figure 1**)[28-41].

General characteristics of the included studies

The general characteristics of the included RCTs can be seen in **Table 1**. We included 13 RCTs for analysis. These RCTs were published from 2011 to 2021. Four studies were done in China, six in Japan, one in Denmark, and the rest in Korea. We analyzed data from four studies reporting results comparing teriparatide *vs* placebo. One study compared alendronate *vs* placebo. Three studies compared zoledronic acid *vs* placebo for spinal fusion surgery. Only one study compared teriparatide combined with denosumab *vs* teriparatide alone for spinal fusion surgery. Two studies compared teriparatide *vs* alendronate. The dose, route and timing of administration of the anti-osteoporotic agents can be seen in **Table 2**.

Risk of bias

Of the 13 studies, only four studies were rated as having a low risk of bias. Five studies were identified as having an unclear risk of bias. The remaining 4 studies were listed as having a high risk of bias. For the randomization process, 4 studies were listed as having a low risk of bias, and the other 9 studies were rated as having an unclear risk of bias. One was rated as having a high risk of bias for deviations from intended interventions, and 7 studies were listed as having an unclear risk of bias. The domain-specific and overall risk of bias of the individual studies can be seen in **Table 3**.

Fusion rate

Ten studies involving 618 patients, including six treatments (risedronate, teriparatide, teriparatide combined with denosumab, zoledronic acid, alendronate and placebo), contributed to the clinical outcome of the fusion rate at final follow-up. The network structure diagrams in **Figure 2 A** detail the direct comparisons between different drugs in the fusion rate. Network meta-analysis showed considerable heterogeneity, with global I^2 =0% (**Figure 2 B**).

In the head-to-head comparison, only teriparatide (OR 3.2, 95% CrI 1.4, 7.8, **Figure 2 C**) was more effective than the placebo in increasing the fusion rate. There was no

statistically significant difference between alendronate *vs* placebo, risedronate *vs* placebo, zoledronic acid *vs* placebo or teriparatide combined with denosumab *vs* placebo in terms of the fusion rate at final follow-up (P>0.05, **Table 3**). The SUCRA was highest for teriparatide combined with denosumab (SUCRA, 90.9%), followed by teriparatide (SUCRA, 74.0%), zoledronic acid (SUCRA, 43.7%), alendronate (SUCRA, 41.1%) and risedronate (SUCRA, 35.0%, **Figure 2 D**).

ODI

Five studies involving 226 patients, including six treatments (risedronate, teriparatide, teriparatide combined with denosumab, zoledronic acid, alendronate and placebo), reported the clinical outcome of the ODI at final follow-up. The network structure diagrams in **Figure 3 A** detail the direct comparisons of ODI between different drugs. Network meta-analysis showed considerable heterogeneity, with global I^2 =0% (**Figure 3 B**).

In the head-to-head comparison, teriparatide (MD -15, 95% CrI -28, -2.7, **Figure 3 C**) and teriparatide combined with denosumab (MD -20, 95% CrI -40, -0.43, **Figure 3 C**) were more effective than the placebo in decreasing the ODI. There was no statistically significant difference between other treatments and placebo in terms of the ODI at final follow-up (P>0.05, **Table 4**).

The SUCRA was highest for teriparatide combined with denosumab (SUCRA, 90.8%), followed by teriparatide (SUCRA, 74.5%), alendronate (SURCA, 52.7), risedronate (SURCA, 52.1%), zoledronic acid (SURCA, 24.2%) and placebo (SURCA, 5.6%, **Figure 3 D**).

We used the node-splitting method and its Bayesian P value to report the inconsistency of our results. For ODI, the confidence intervals from direct and indirect evidence were generally consistent, with minor differences (all P>0.05, **Figure 4**).

Adverse events

Four studies involving 252 patients, testing four treatments (risedronate, teriparatide, alendronate and placebo), contributed to the clinical outcome of the adverse events. The network structure diagrams in **Figure 5 A** illustrate the direct

comparisons of different drugs on adverse events. Network meta-analysis showed considerable heterogeneity, with global I^2 =0% (**Figure 5 B**).

In the head-to-head comparison, there was no statistically significant difference between any anti-osteoporosis drugs and placebo in terms of adverse events (P>0.05, **Table 5**, **Figure 5 C**).

The SUCRA of teriparatide combined with denosumab was highest (SUCRA, 85.6%), followed by risedronate (SUCRA, 62.0%), teriparatide (SURCA, 27.1%) and alendronate (SURCA, 25.**3%, Figure 5 D**).

DISCUSSION

This is the first network meta-analysis comparing different anti-osteoporosis drugs for spinal fusion surgery patients. Our network meta-analysis included 13 RCTs and compared different anti-osteoporosis drugs on fusion rate, ODI and adverse events after spinal fusion surgery. A total of 592 patients were treated with 6 therapeutic methods, including risedronate, teriparatide, teriparatide combined with denosumab, zoledronic acid, alendronate and placebo.

Teriparatide combined with denosumab and teriparatide alone ranked as the most and second most preferable anti-osteoporosis drug, with higher fusion rates and lower ODIs. Moreover, adverse events did not differ among these groups. These results may help orthopedic surgeons select anti-osteoporosis drugs for spinal fusion surgery patients. In comparison to prior meta-analyses, a key advantage of this network meta-analysis lies in its thorough search strategy and its analysis of the safety and effectiveness of various pharmacological treatments across a larger network of studies and sample size. Additionally, the study features a strong design that allows for the ranking of treatments based on their effects on the desired outcome.

Interestingly, no significant treatment effect of bisphosphonates (risedronate, zoledronic acid and alendronate) was observed on the spinal fusion rate. Previously, a pairwise meta-analysis compared bisphosphonate and teriparatide use in thoracolumbar spinal fusion[42]. They revealed that bisphosphonates had no effects on

the spinal fusion rate compared with the control. In contrast, some researchers reached the opposite conclusion about bisphosphonates for the fusion rate in spinal fusion surgery patients. Met *et al*[23] conducted an updated meta-analysis and found that postoperative bisphosphonates did not significantly alter the fusion rate after lumbar spinal fusion. Govindarajan *et al*[43] conducted a meta-analysis and demonstrated the independent benefits of bisphosphonate therapy in accelerating the fusion rate after spinal surgery. These two meta-analyses had common drawbacks of combining these bisphosphonates as a pooled group for analysis. In this network meta-analysis, we separated these bisphosphonates for analysis and ranked their effects.

Implications for Clinical Practice

The UK National Institute for Clinical Excellence (NICE) guidelines recommend teriparatide as an alternative treatment in the prevention of osteoporotic fragility fractures in postmenopausal women[44]. According to the American College of Physicians (ACP), clinicians should consider denosumab as a secondary pharmacological option for reducing fracture risk in postmenopausal women with primary osteoporosis who are unable to take bisphosphonates due to contraindications or adverse effects[45]. From our network meta-analysis, we recommend teriparatide combined with denosumab as the first choice for increasing the fusion rate. Only one study compared teriparatide combined with denosumab *vs* teriparatide with a small sample size. Therefore, care should be taken when interpreting these results.

Limitations

5

This study does have several limitations that need to be considered when interpreting the findings. First, the major concern of this network meta-analysis is the inclusion of drugs with different doses and treatment durations, which lessens the robustness and reliability of the results and conclusions. Second, subgroup analysis was not done due to the number of included studies. Future studies could compare subgroups of fusion level, drug dose, and drug duration. Third, potential confounding factors (e.g., smoking status, obesity, and initial osteoporotic status) were not accounted for and might influence the results. In addition, a wide range of mean ages, the

prevalence of females and Asians, and follow-up time data increased the heterogeneity between studies.

CONCLUSION

This network meta-analysis suggests that teriparatide combined with denosumab and teriparatide alone significantly can increase the fusion rate and decreased the ODI without increasing adverse events. Based on current evidence, teriparatide combined with denosumab or teriparatide alone is recommended to increase the fusion rate and to reduce the ODI in spinal fusion patients. However, the overall quality of evidence is low, and the overall certainty of the synthesized evidence is low. There is a need for more high-quality RCTs to reassess or confirm this conclusion.

ARTICLE HIGHLIGHTS

Research background

Administering anti-osteoporotic agents to patients perioperatively is a widely accepted approach for improving bone fusion rates and reducing the risk of complications. The best anti-osteoporotic agents for spinal fusion surgery remain unclear.

Research motivation

This network meta-analysis suggests that teriparatide combined with denosumab and teriparatide alone significantly can increase the fusion rate and decreased the ODI without increasing adverse events.

Research objectives

The purpose of this study was to investigate the efficacy and safety of different anti-osteoporotic agents in spinal fusion surgery *via* network meta-analysis.

Research methods

Searches were conducted in four electronic databases (PubMed, EMBASE, Web of Science, the Cochrane Library and China National Knowledge Infrastructure (CNKI)) from inception to November 2022. Any studies that compared anti-osteoporotic agents *vs* placebo for spinal fusion surgery were included in this network meta-analysis. Outcomes included fusion rate, Oswestry disability index (ODI), and adverse events. Network meta-analysis was performed by R software with the gemtc package.

Research results

In total, 13 RCTs were included in this network meta-analysis. Only teriparatide (OR 3.2, 95% CrI 1.4, 7.8) was more effective than placebo in increasing the fusion rate. The surface under the cumulative ranking curve (SUCRA) of teriparatide combined with denosumab was the highest (SUCRA, 90.9%), followed by teriparatide (SUCRA, 74.0%), zoledronic acid (SUCRA, 43.7%), alendronate (SUCRA, 41.1%) and risedronate (SUCRA, 35.0%). Teriparatide (MD -15, 95% CrI -28, -2.7) and teriparatide combined with denosumab (MD -20, 95% CrI -40, -0.43) were more effective than placebo in decreasing the ODI. The SUCRA of teriparatide combined with denosumab was highest (SUCRA, 90.8%), followed by teriparatide (SUCRA, 74.5%), alendronate (SURCA, 52.7), risedronate (SURCA, 52.1%), zoledronic acid (SURCA, 24.2%) and placebo (SURCA, 5.6%) for ODI. The adverse events were not different between groups.

Research conclusions

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Research perspectives

Teriparatide combined with denosumab or teriparatide alone is recommended to increase the fusion rate and to reduce ODI in spinal fusion patients.

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