

Synergistic effects of Xianlinggubao, vitamin D and alendronate sodium on pain relief, bone metabolism and prosthesis stability in post-hip arthroplasty patients

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Abstract: This study investigated the combined effects of Xianlinggubao, a traditional Chinese herbal medicine, with vitamin D and alendronate sodium on pain management, bone metabolic health, and prosthetic survival in patients post-hip arthroplasty. A total of 104 patients were randomly assigned into treatment group, which additionally received Xianlinggubao and control group, which received standard postoperative care along with vitamin D and alendronate. Key outcomes, including Visual Analog Scale (VAS) scores, Traditional Chinese Medicine (TCM) syndrome scores, Harris hip scores and bone metabolism markers, were evaluated over six months. The Xianlinggubao group showed significant improvement in hip function and pain reduction, evidenced by higher Harris hip scores and lower VAS and TCM syndrome scores. Bone metabolism indicators such as 25-hydroxyvitamin D, bone-specific alkaline phosphatase, and osteocalcin were elevated, while markers of bone resorption decreased more significantly in the treatment group. These findings suggested that Xianlinggubao, when combined with vitamin D and alendronate sodium, offered a complementary therapeutic approach to enhance recovery outcomes in hip arthroplasty patients by improving bone metabolism, reducing pain and supporting prosthetic stability. Further research with larger cohorts was recommended to confirm these benefits.

Keywords: Xianlinggubao; vitamin D; alendronate sodium; hip arthroplasty; pain; bone metabolism; prosthetic survival

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INTRODUCTION

Hip replacement surgery is a common clinical method used to treat femoral neck fractures, femoral head necrosis, late-stage rheumatoid arthritis and osteoarthritis, which can achieve satisfactory reduction and joint function (Petis *et al.*, 2015). However, patients who undergo hip replacement surgery often have osteoporosis, and long-term bed rest after surgery can exacerbate osteoporotic symptoms. Osteoporosis can also affect fracture healing and even lead to complications such as loosening of the prosthesis and re-fracture. Therefore, active anti-osteoporosis intervention should be given on the basis of hip replacement surgery (Schache *et al.*, 2016). Vitamin D and alendronate sodium are commonly used clinical anti-osteoporosis drugs, which can improve bone metabolism and reduce bone loss, but the overall efficacy is not ideal (Simpson *et al.*, 2020).

According to the theories of traditional Chinese medicine (TCM), surgical incisions can cause tendon injuries, bone fractures, obstruction of Qi and blood circulation and stagnation of meridians. Osteoporosis belongs to the category of bone impediment and is often caused by insufficient kidney essence and bone marrow nourishment. The treatment principle focuses on nourishing the kidneys, promoting blood circulation, strengthening tendons, and tonifying bones (Ji *et al.*, 2013). Xianlinggubao is a commonly used traditional Chinese medicine in clinical practice for treating osteoporosis, fractures, osteoarthritis,

and aseptic necrosis of bones. It has the effects of nourishing the kidneys, strengthening bones, promoting blood circulation and opening up the meridians (Kwon *et al.*, 2023). This study aimed to explore the effects of combining Xianlinggubao with vitamin D and alendronate sodium on pain, bone metabolism status, and prosthesis survival in patients after hip arthroplasty.

MATERIALS AND METHODS

The study was approved by the ethics committee of the hospital, and all participants provided signed written informed consent prior to their inclusion in the study. This ensured that ethical standards were maintained throughout the research process.

Study design and study settings

This study was a randomized controlled trial conducted at the PLA Rocket Force Characteristic Medical Center in Beijing, China, from May 2021 to July 2023. A total of 104 patients who underwent unilateral hip replacement surgery were enrolled and randomly assigned to two groups: the Conventional Group and the Xianlinggubao Group, each consisting of 52 patients. The Conventional Group received standard postoperative care, including vitamin D and alendronate sodium, while the Xianlinggubao Group received the same standard care along with Xianlinggubao capsules. The patient screening process is shown in fig. 1.

Inclusion criteria and exclusion criteria

The study inclusion criteria were as follows: (1) Unilateral

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hip replacement surgery performed by the same group of physicians. (2) No history of previous hip replacement surgery. (3) Meeting the osteoporosis criteria, with a bone density test showing T-score less than -2.5 (2022). (4) Age of 55 to 80 years. (5) Meeting the criteria for Kidney Yang Deficiency outlined in the Clinical Research Technical Guidelines for New Traditional Chinese Medicine in the Treatment of Primary Osteoporosis (Meng *et al.*, 2018). (6) Signed informed consent form. Patients were ineligible if they met the following exclusion criteria: (1) Presence of acute or chronic infections, or occult active infections. (2) Open growth plates. (3) Use of anti-osteoporosis medications within the past 3 months. (4) Congenital lower limb deformities. (5) Pregnant or lactating patients. (6) Significant functional disorders of major organs. (7) Presence of immune or hematological systemic diseases. (8) Allergic constitution.

Treatment methods

The conventional group received routine postoperative treatment, including intravenous patient-controlled analgesia for 48 hours, intravenous administration of antibiotics for infection prophylaxis for 7 days, and subcutaneous injection of low molecular weight heparin for anticoagulation for 10 days. The patients were placed in a supine position with the affected limb in a neutral position, with a soft pillow placed between the legs. Postoperatively, rehabilitation training was conducted according to medical advice. Starting from the second day after surgery, vitamin D3 (produced by Wyeth Pharmaceutical Co., Ltd., Suzhou, China) and sodium alendronate (produced by Shiyao Group Ouyi Pharmaceutical Co., Ltd., Shijiazhuang, China) were administered for anti-osteoporosis treatment. Vitamin D3 was orally taken at a dose of 125 IU per intake, twice daily. Sodium alendronate was orally taken at a dose of 10 mg per intake, twice daily (Kwon *et al.*, 2023). The treatment duration was at least 6 months.

In addition to the conventional treatment, the Xianlinggubao group received Xianlinggubao capsules (produced by Tongjitang Guizhou Pharmaceutical Co., Ltd., Guiyang, China) for treatment. Xianlinggubao is a traditional Chinese medicine formulation primarily composed of several key herbs. The main ingredients include: Epimedium, Xu Duan, Bu Gu Zhi, Zhimu, Dihuang, Danshen (Bao, Hangsheng *et al.*, 2020). Xianlinggubao capsules were orally taken at a dose of 1.5 g per intake, twice daily.

Scoring criteria

Visual Analog Scale (VAS) score

The scale ranges from 0 to 10, with 10 being the highest score indicating unbearable severe pain. The lower the score, the milder the pain.

Traditional chinese medicine (TCM) syndrome score

The main symptom is low back pain, with a score of 0-6.

Secondary symptoms include lumbago and weakness of the knees, aversion to cold and preference for warmth, frequent urination and loose stools, with a score of 0-3. A normal tongue and pulse score 0 points, while abnormalities score 1 point. The score for the main symptoms + the score for the secondary symptoms + the score for the tongue and pulse = total score.

Harris hip score

It consists of daily activities, walking ability, range of motion and pain. The score is calculated on a percentage basis, with higher scores indicating better hip joint function (Chiarotto *et al.*, 2019).

Efficacy criteria

Efficacy assessment is determined using the Harris Hip Score: scores of 90 or above are considered as excellent, 80-89 as good, 70-79 as fair and below 70 indicating poor (He *et al.*, 2022).

Detection methods

Peripheral venous blood samples (5 ml) were collected from patients in both groups before the start of treatment and six months afterward. The samples were stored at 4°C for 30 minutes, followed by centrifugation at 3000 rpm for 10 minutes to extract the serum. The concentration of 25-hydroxyvitamin D [25(OH)D] was determined using a high-performance liquid chromatography (HPLC) system (Shimadzu LC-2050, Japan).

Key bone metabolism markers-including bone-specific alkaline phosphatase (BALP), osteocalcin (BGP), N-terminal propeptide of type I procollagen (PINP), tartrate-resistant acid phosphatase-5b (TRACP-5b) and C-terminal telopeptide of type I collagen (β -CTX)—were measured through a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). Reagents for the assays were supplied by Shanghai Yiyuan Biotechnology Co., Ltd. (Shanghai, China) and data were collected with a Thermo Fisher MK3 microplate reader (Waltham, MA, USA). Furthermore, the rates of prosthesis survival, wound infections, deep vein thrombosis (DVT) in the lower limbs, hematomas at the incision site, and nerve injuries were systematically recorded for both groups.

Ethical approval

This study was approved by the ethics committee of PLA Rocket Force Characteristic Medical Center (22-PLA-EC-910). Signed written informed consents were obtained from the patients and/or guardians.

STATISTICAL ANALYSIS

SPSS 25.0 was adopted for the data analysis. It has been confirmed that bone metabolism factors and Harris Hip Score are normally distributed and meet the requirements of homogeneity of variance. The measurement indicators

are expressed as ($\bar{x} \pm s$) and the paired t-test is used for comparison. Descriptive statistics are used for count data, and the χ^2 test is used for comparison. When the theoretical frequency is ≥ 1 and ≤ 5 , a corrected test is used. A p-value of less than 0.05 is considered to indicate a significant difference.

RESULTS

Baseline information

In the Conventional Group, ages ranged from 50 to 78 years (mean = 62.92 ± 5.94 years), with osteoporosis durations from 1 to 8 years (mean = 5.35 ± 1.03 years). The group consisted of 31 males and 21 females, with primary diagnoses of femoral neck fractures (28 cases), rheumatoid arthritis (11 cases) and osteoarthritis (13 cases). Hip replacements were performed on the left side in 28 cases and the right side in 24 cases. In the Xianlinggubao Group, patients' ages ranged from 50 to 80 years (mean = 63.47 ± 6.85 years) and osteoporosis duration from 1 to 8 years (mean = 5.27 ± 1.12 years). This group had 29 males and 23 females, with primary diagnoses of femoral neck fractures (30 cases), rheumatoid arthritis (8 cases), and osteoarthritis (14 cases). Hip replacements were performed on the left side in 25 cases and the right side in 27 cases.

Comparing VAS scores, TCM syndrome scores and Harris Hip Scores between two groups

Before treatment, there were no significant differences in VAS scores, TCM syndrome scores, or Harris Hip Scores between the two groups ($P > 0.05$). Following treatment, both groups demonstrated improvements, with Harris Hip Scores increasing and VAS and TCM syndrome scores decreasing compared to baseline. Moreover, the Xianlinggubao group exhibited significantly higher Harris Hip Scores and lower VAS and TCM syndrome scores compared to the conventional group ($P < 0.05$). Detailed data can be found in table 1.

Comparing the efficacy between two groups

In the Xianlinggubao group, there were 19 cases with excellent outcomes and 23 cases with good outcomes, resulting in an excellent and good rate of 80.77%, which was significantly higher than the conventional group rate of 61.54% (12 cases with excellent outcomes and 19 cases with good outcomes) ($P < 0.05$). Detailed information was shown in table 2 and fig. 2.

Comparing bone metabolism indicators between two groups

Following the treatment, both the Xianlinggubao and conventional groups exhibited notable improvements, with elevated levels of 25(OH)D, BALP and BGP and reduced levels of PINP, TRACP-5b and β -CTX. However, after treatment, the Xianlinggubao group demonstrated significantly higher levels of 25(OH)D, BALP and BGP, along with significantly lower levels of PINP, TRACP-5b,

and β -CTX when compared to the conventional group ($P < 0.05$). The comprehensive results are provided in table 3.

Comparing prosthetic survival between two groups

In the Xianlinggubao group, there were 49 cases of prosthetic survival, resulting in a prosthetic survival rate of 94.23%. This rate was compared to the conventional group's prosthetic survival rate of 88.46% (46 cases), and there was no statistically significant difference ($P > 0.05$). Detailed information was shown in table 4.

Comparison of complication rates between the two groups

The complication rate in the conventional group was 9.62%, compared to 3.85% in the Xianlinggubao group. However, the difference between the two groups was not statistically significant ($P > 0.05$). Further details are presented in table 5.

DISCUSSION

Hip replacement surgery emerged in the 1940s and was introduced in China after the 1960s. After several decades of development, the technique has become highly mature, and the prosthetic materials have become increasingly advanced. It has now become a commonly used procedure for clinically treating hip joint disorders (Ackerman *et al.*, 2021). The hip joint is an important weight-bearing joint in the human body with a unique anatomical structure. The healing process after hip replacement surgery is relatively long and there is often an increase in stress on the femur. Combined with the impact of pre-existing diseases, postoperative osteoporosis is a common phenomenon. Therefore, some patients still experience issues such as pain and loosening of the prosthesis after surgery (Agarwal *et al.*, 2021). Currently, a combination of vitamin D and alendronate sodium is commonly used for postoperative anti-osteoporosis treatment. Vitamin D promotes calcium absorption, while alendronate sodium improves bone metabolism and promotes osteoblast activity. The combined use of these two medications can effectively counteract osteoporosis to a certain extent (Barrionuevo *et al.*, 2019).

According to the theories of traditional Chinese medicine (TCM), the kidneys are believed to govern the bones, and kidney deficiency is considered the main cause of bone atrophy. As early as in the book "Ling Shu · Pathogenic Factors and Organ-Malformation Diseases: When the kidney pulse is weak and smooth, it leads to bone atrophy, making it difficult for the person to rise from a seated position" (Fink *et al.*, 2019). After hip replacement surgery, the syndrome of qi deficiency and blood stasis can worsen, further damaging the kidney qi and aggravating bone atrophy. Xianlinggubao capsules are commonly used TCM compound preparations for the clinical treatment of osteoporosis-related diseases.

Table 1: Comparing VAS scores, TCM syndrome scores and Harris hip Scores between two groups

Group	VAS scores		TCM syndrome scores		Harris hip scores	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Conventional group	6.54±1.11	4.35±0.92*	14.25±2.59	7.25±1.44*	50.14±4.77	73.36±5.59*
Xianlinggubao group	6.48±1.17	3.08±0.74*	14.16±2.74	4.89±1.10*	49.86±5.05	85.68±5.04*
t	0.268	7.757	0.172	9.392	0.291	11.804
P	0.789	0.000	0.864	0.000	0.772	0.000

*Compared to the same group before treatment, $P < 0.05$.

Table 2: The efficacy between two groups.

Group	Excellent	Good	Fair	Poor	Excellent and good rate
Conventional group	12	19	13	8	31(61.54)
Xianlinggubao group	19	23	6	4	42(80.77)
χ^2					5.561
P					0.018

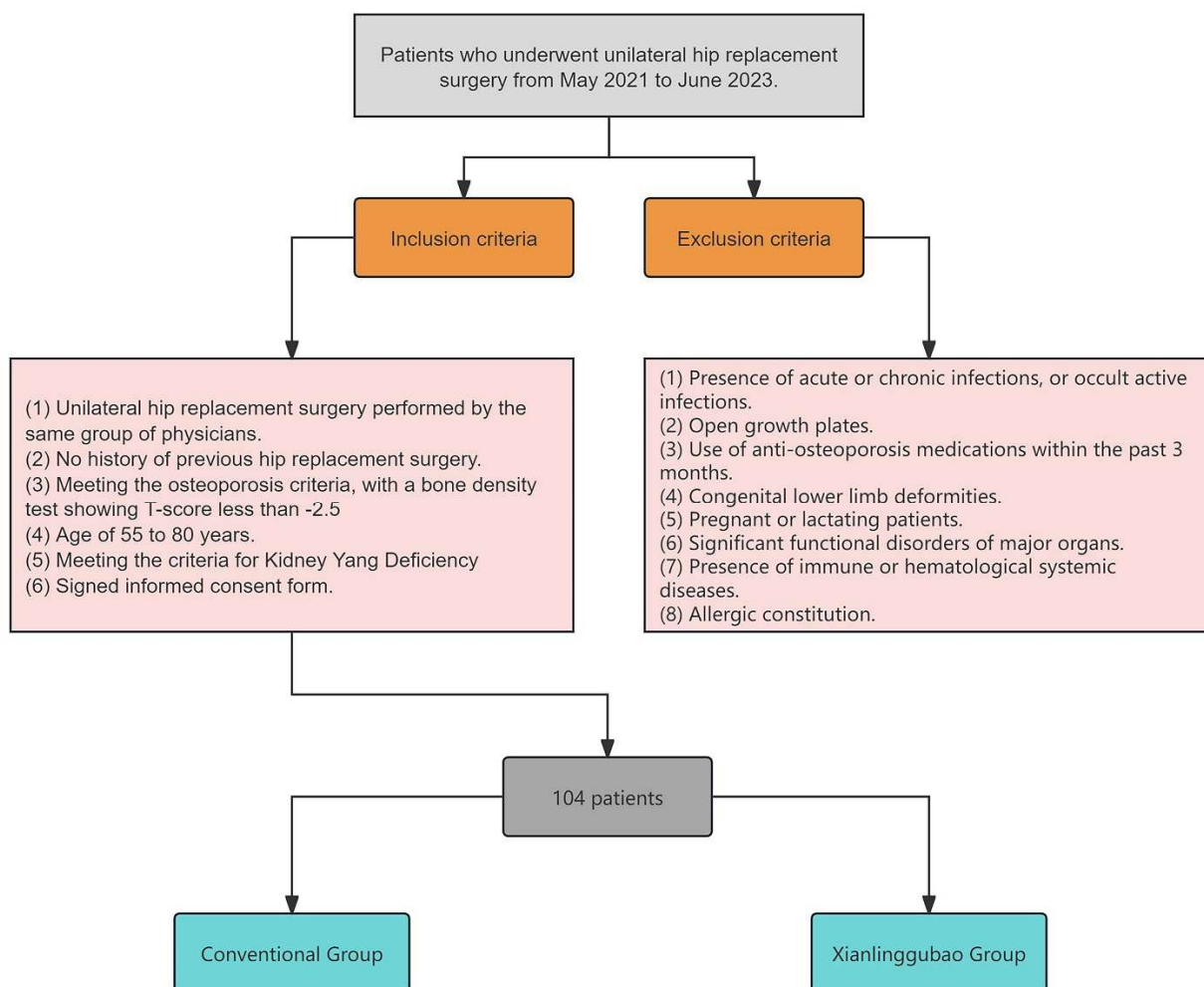


Fig. 1: Patient selection flowchart

Table 3: Comparing bone metabolism indicators between two groups

Group	25(OH)D (ng/mL)		PINP (ng/mL)		TRACP-5b (U/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Conventional group	18.96±3.42	22.76±4.01	50.12±5.86	45.87±5.32	3.01±0.15	1.15±0.13
Xianlinggubao group	19.11±3.53	25.85±4.56	48.97±5.77	42.16±4.78	2.97±0.18	0.94±0.11
t	0.220	3.669	1.008	3.741	1.231	8.892
P	0.826	0.000	0.316	0.000	0.221	0.000
Group	BALP (pg/mL)		BGP (ng/L)		β-CTX (ng/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Conventional group	20.45±2.59	27.52±2.89	7.56±1.25	8.26±1.33	0.59±0.12	0.46±0.10
Xianlinggubao group	20.16±2.73	34.76±3.04	7.49±1.33	9.87±1.37	0.60±0.13	0.35±0.09
t	0.556	12.447	0.277	6.080	0.408	5.896
P	0.580	0.000	0.783	0.000	0.684	0.000

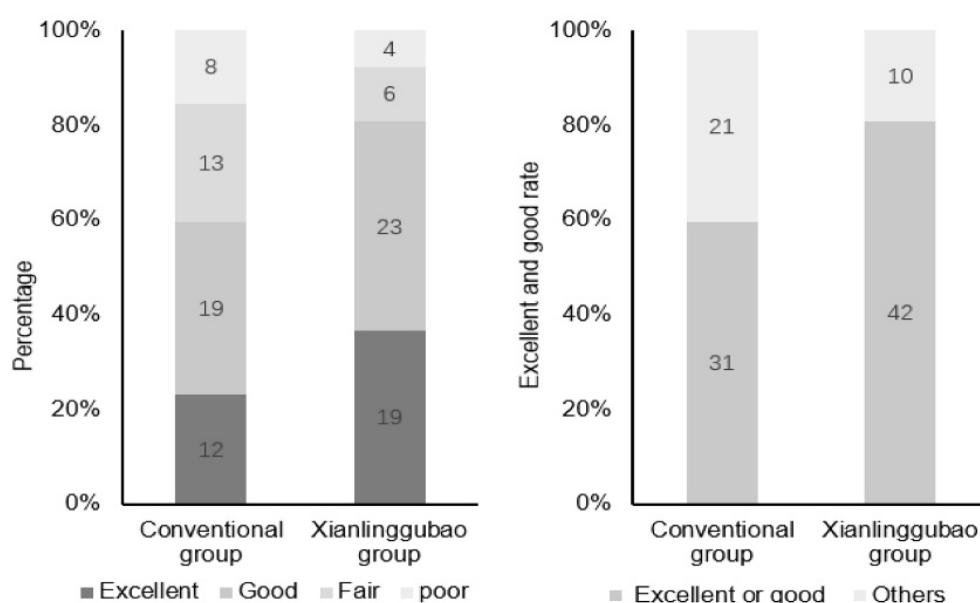
*Compared to the same group before treatment, $P < 0.05$.

Table 4: Comparing prosthetic survival between two groups

Group	Prosthetic survival	Rate
Conventional group	46	88.46
Xianlinggubao group	49	94.23
χ^2	1.095	
P	0.295	

Table 5: Comparing the incidence of complications between two groups

Group	Incision infection	Lower limb venous thrombosis	Incision hematoma	Nerve injury	Total rate (%)
Conventional group	2	1	2	0	5(9.62)
Xianlinggubao group	1	0	1	0	2(3.85)
χ^2					0.613
P					0.434

**Fig. 2:** The efficacy between two groups.

The key herb in the formula is Epimedium, which excels in tonifying the kidneys, strengthening yang, and nourishing bones and marrow. Xu Duan is good at supplementing and nourishing the liver and kidneys, strengthening tendons, and invigorating bones, while Bu Gu Zhi is effective in tonifying yang and the kidneys, consolidating essence and reducing urine frequency. The combination of these two herbs enhances the effects of nourishing the liver and kidneys, strengthening tendons, and promoting bone health. The formula is also supplemented with Zhimu and Dihuang, which nourish yin, moisten dryness, clear heat, and cool the blood, aiming to achieve the concept of seeking yang within yin by nourishing the kidney yin to support the kidney yang. Danshen is included as an assistant herb to promote blood circulation, dispel stasis, nourish the blood, and calm the spirit. The overall formula focuses on nourishing the kidneys and strengthening bones, while also promoting blood circulation and dispelling stasis (Xiao *et al.*, 2022).

This study found that compared to before treatment, both groups showed an increase in Harris hip scores and a decrease in VAS scores and TCM syndrome scores. The group treated with Xianlinggubao capsules had higher Harris hip scores and lower VAS scores and TCM syndrome scores compared to the control group. The excellent rate of efficacy was also higher in the Xianlinggubao group than in the control group. These results suggest that the combination of Xianlinggubao capsules, vitamin D, and alendronate sodium can alleviate pain and TCM symptoms, improve hip joint function, and enhance the effectiveness of treatment after hip replacement surgery. This is because the icariin and total flavonoids contained in Xianlinggubao capsules can improve bone metabolism, promote the maturation of new bone cells, and facilitate fracture healing. The alkaloids and volatile oils in Xu Duan have analgesic and hemostatic effects, and it also contains a large amount of calcium, which promotes bone growth and prevents bone loss (Zeng *et al.*, 2022; Vukicevic *et al.*, 2016). The epimedium glycoside in Bu Gu Zhi promotes osteogenic induction and differentiation, inhibits apoptosis of osteoclasts and facilitates fracture healing and repair (Wang *et al.*, 2019). The schisandrin A-III in Zhimu inhibits platelet aggregation, adhesion, and activation, prevents thrombus formation, and improves blood flow perfusion at the surgical site (Liu *et al.*, 2022). The salvianolic acid in Danshen inhibits oxidative stress damage, improves local microcirculation and nutrient metabolism and accelerates tissue repair of injuries (He *et al.*, 2022).

In individuals with osteoporosis, the activity of osteoclasts outpaces that of osteoblasts, leading to disrupted bone metabolism. 25-hydroxyvitamin D (25(OH)D) plays a crucial role in enhancing the absorption of calcium and phosphorus in the gut, which supports bone formation and mineralization (Li *et al.*, 2021). Key markers of osteoblast

activity, such as bone-specific alkaline phosphatase (BALP) and osteocalcin (BGP), contribute to the mineralization of the bone matrix and reflect osteoblast function (Zhang and Hu, 2016). Procollagen type I N-terminal propeptide (PINP), a byproduct of collagen type I synthesis by osteoblasts, serves as a reliable indicator of osteoblast activity (Cosman *et al.*, 2011). On the other hand, tartrate-resistant acid phosphatase-5b (TRACP-5b), an enzyme secreted by osteoclasts, plays a central role in bone resorption (2021). Additionally, the β -C-terminal telopeptide of type I collagen (β -CTX), a degradation fragment of type I collagen, serves as a marker for osteoclast activity (Wen *et al.*, 2022).

The findings of this study indicate that both the Xianlinggubao and conventional groups experienced improvements in bone metabolism markers, with increased levels of 25(OH)D, BALP, and BGP, and decreased levels of PINP, TRACP-5b and β -CTX compared to baseline. Notably, the Xianlinggubao group showed significantly higher levels of 25(OH)D, BALP, and BGP, and lower levels of PINP, TRACP-5b and β -CTX compared to the conventional group ($P < 0.05$). These results suggest that the combination of Xianlinggubao capsules, vitamin D, and alendronate sodium effectively enhances bone metabolism after hip replacement surgery, which in turn contributes to improved patient recovery and pain reduction. The active ingredients in Xianlinggubao capsules, including kidney-tonifying and bone-strengthening herbs like Epimedium, Xu Duan and Bu Gu Zhi, may promote the osteogenic differentiation of mesenchymal stem cells in bone marrow, enhance osteoblast mineralization and induce osteoclast apoptosis, thereby inhibiting bone resorption.

Although the Xianlinggubao group showed a higher implant survival rate and a lower incidence of complications compared to the control group, these differences were not statistically significant. This may be attributed to the relatively small sample size (52 patients per group). Larger-scale studies are needed to assess whether Xianlinggubao can improve implant survival rates and reduce complication incidences.

In conclusion, the combination of Xianlinggubao capsules combined with vitamin D and alendronate sodium can alleviate pain, improve bone metabolism, promote implant survival and enhance therapeutic efficacy in patients with hip replacement surgery.

CONCLUSION

This study demonstrates that the combination of Xianlinggubao capsules with vitamin D and alendronate sodium significantly enhances recovery outcomes in patients following hip arthroplasty. The treatment group exhibited notable improvements in pain relief, hip joint function, and bone metabolism markers compared to the

conventional group. Specifically, the Xianlinggubao group showed higher Harris Hip Scores, lower VAS and TCM syndrome scores and more favorable changes in bone metabolism indicators such as increased 25-hydroxyvitamin D, BALP and BGP, alongside reduced levels of bone resorption markers. These findings suggest that Xianlinggubao, when integrated with standard anti-osteoporosis therapies, offers a complementary approach to improving postoperative recovery, reducing pain, and supporting prosthetic stability. While the study did not find statistically significant differences in prosthetic survival or complication rates, the overall efficacy and safety of the combined treatment highlight its potential as a valuable therapeutic strategy. Further research with larger cohorts is recommended to validate these benefits and explore long-term outcomes.

Conflict of interest

The authors declared no conflict of interest.

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