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Original Article

Efficacy of total knee arthroplasty combined with Yunnan Baiyao in the treatment of knee osteoarthritis and their effects on serum expression of IL-6, TNF-α, VCAM-1 and MMP-9 in patients

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Abstract: Objective: This study aimed to explore the efficacy of total knee arthroplasty combined with Yunnan Baiyao in the treatment of knee osteoarthritis and their effects on serum expression of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), vascular cell adhesion molecule-1 (VCAM-1), and matrix metalloproteinase-9 (MMP-9) in patients. Methods: We randomly assigned 110 knee osteoarthritis patients treated in the department of orthopedics in TsingTao Chest Hospital from January 2017 to June 2019 to receive oral Yunnan Baiyao (2 capsules/time, 4 times a day) combined with total knee arthroplasty (the observation group, OG, 55 cases) or to receive total knee arthroplasty alone (the control group, CG, 55 cases). Serum expression levels of inflammatory cytokines (IL-6, TNF-α, VCAM-1, and MMP-9) were measured before and after surgery. The two groups were compared in the scores of pain and swelling, the postoperative recovery, and the quality of life at 1 month after surgery. Results: One month after surgery, the expression levels of IL-6, TNF-α, VCAM-1, and MMP-9, and the scores of pain and swelling in the two groups were markedly reduced compared with those before treatment ($P<0.05$), and the reductions were more sharp in OG than in CG ($P<0.05$). The quality of life one month after surgery was better in OG than in CG ($P<0.05$). Conclusion: Total knee arthroplasty combined with Yunnan Baiyao can relieve the pain and swelling, promote the clearance of inflammatory cytokines, and enhance the postoperative quality of life of patients with knee osteoarthritis.

Keywords: Total knee arthroplasty, knee osteoarthritis, Yunnan Baiyao, inflammatory factors, efficacy

Introduction

The onset of knee osteoarthritis is closely related to degenerative changes in the knee joint and wears at the joints. Knee osteoarthritis is induced by degenerative changes in articular cartilage and local hyperplasia which causes comorbid joint effusions and deformities, marking one of the main causes of knee pain and walking disorders in the elderly [1, 2]. Advanced severe knee osteoarthritis is mainly treated by total knee arthroplasty. The latest data released by the USA predicted an increase in the annual cases of patients undergoing total knee arthroplasty to 3.4 million by 2030, as well as a rise in the economic expenditures on the surgery and subsequent supportive treatment [3-5]. Advancements in the scientific technology, surgical materials, surgical techniques, together with postoperative follow-up and close monitoring, all contribute to improvements in the recovery of patients receiving total knee arthroplasty, but 20% of patients still have poor responses to the surgical treatment [6]. The development and progression of knee osteoarthritis are closely related to the production of multiple inflammatory cytokines and their complex signaling pathways [7]. Studies have confirmed that the promoted differentiation of osteoclasts by inflammatory responses can result in bone destruction. Increased serum levels of inflammatory cytokines after knee arthroplasty can hinder wound healing and impair knee functions of patients. Therefore, reducing damages

caused by inflammatory cytokines and relieving postoperative inflammatory responses are beneficial to the postoperative recovery of patients [8]. The levels of inflammatory cytokines remain high in patients just after total knee arthroplasty until 18 months later when their levels tend to normal [9]. Inflammatory cytokines often induce postoperative infection. Periprosthetic infection after total knee arthroplasty is a common complication and one of the important reasons for subsequent revision total knee arthroplasty, causing serious secondary injuries and heavy economic burden [10]. The release of inflammatory cytokines after total knee arthroplasty results in bone destruction and physical pain, as well as joint effusions and joint swelling [2]. Yunnan Baiyao is a traditional Chinese medicine preparation that has been used to activate blood circulation, disperse blood stasis, alleviate pain, and stop bleeding for a long history. It can inhibit the arachidonic acid metabolism pathway in bone cells and reduce the production of inflammatory cytokines to reduce clinical symptoms of rheumatoid arthritis in rats [11]. A domestic study found that total knee arthroplasty combined with Yunnan Baiyao can significantly decrease the expression of inflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP)) and improve postoperative recovery [12]. Here we also observed the expression of other inflammatory cytokines (vascular cell adhesion molecule-1 (VCAM-1) and matrix metalloproteinase-9 (MMP-9)). On the basis of the above study, we studied the effect of total knee arthroplasty combined with Yunnan Baiyao on postoperative efficacy and the expression of various inflammatory cytokines, hoping to provide more effective data to support the clinical research.

Materials and methods

General information

We randomly assigned 110 knee osteoarthritis patients (67 males and 43 females, aged 60-70 years, with an average age of 64.0± 5.8.110 years) treated in the department of orthopedics in TsingTao Chest Hospital from January 2017 to June 2019 to receive oral Yunnan Baiyao combined with total knee arthroplasty (the observation group, OG, 55 cases) or to receive total knee arthroplasty alone (the control group, CG, 55 cases). OG was composed of 34 males and 21 females, with an average age of 64.2±5.5 years. CG was composed of 33 males and 22 females, with an average age of 63.8±5.7 years. This study was approved by the ethics committee of TsingTao Chest Hospital. All patients signed the written informed consent.

Inclusion and exclusion criteria

Inclusion criteria: 1. Patients diagnosed with knee osteoarthritis according to the diagnostic criteria in the Guidelines for the Diagnosis and Treatment of Osteoarthritis (2007) and Kellgren-Lawrence (KL) classification criteria [13, 14]. 2. Patients with surgical indications for total knee arthroplasty. 3. Patients with a well-functioning ligament. 4. Patients with no symptoms of systemic or local infection. 5. Patients with complete clinical data and willing to cooperate with the follow-up. Exclusion criteria: 1. Patients with rheumatoid arthritis. 2. Patients with severe heart, liver, kidney and other diseases. 3. Patients with generalized ligamentous laxity. 4. Pregnant or lactating women. 5. Patients with difficulties in participating in the follow-up. 6. Patients with a history of allergies to Yunnan Baiyao capsules.

Methods

All patients received total knee arthroplasty. After surgery, patients from CG were given conventional anti-infective and hemostatic treatments. Besides conventional treatments, patients from OG were also given Yunnan Baiyao capsules (0.25 g/capsule, Yunnan Baiyao Group Co., Ltd., China) at a dose of 0.5 g/time, four times a day, from the first day after surgery, 4 weeks as a cycle. Oral Yunnan Baiyao was ordered during the hospitalization. After discharge, drug administration was checked every week by the outpatient review or via the telephone. Any allergies or intolerance of Yunnan Baiyao can call on a drug withdrawal and exclude patients from our study.

Outcome measures

Primary outcome measures: Before surgery and one month after surgery, 5 mL of venous blood was collected from each patient at 8 a.m. and stored in sterilized tubes containing ethylenediamine tetraacetic acid (Shanghai Heng-

Yuan Biological Technology Co., Ltd., China) in a 4°C refrigerator for 15 minutes. Then, blood samples were centrifuged at 3300 rpm/min to separate the serum. The serum was mixed with 40 μL of protease inhibitor phosphate buffer solution (Shanghai HengYuan Biological Technology Co., Ltd., China) and stored in a -80°C refrigerator. Serum expressions of IL-6, TNF-α, VCAM-1, and MMP-9 were measured using the enzyme-linked immunosorbent assay with a fully automatic multi-functional microplate reader (Thermo Fisher Scientific Inc, USA). All kits were purchased from Shanghai HengYuan Biological Technology Co., Ltd. (China).

Two weeks after total knee arthroplasty, the pain and swelling of the surgery area were assessed and scored according to the quantitative classification [15]: 0 point for grade 0, 2 points for grade 1, 4 points for grade 2, 6 points for grade 3. A higher grade and score indicated a higher intensity of pain and swelling. The assessment was conducted by the same physician to ensure the accuracy of scoring.

Postoperative pain scoring: The subjective pain sensation was quantified by the linear visual analogue scale (VAS). On a 10 cm scale of 0 to 10, 0 meant "no pain" and 10 meant "the worst possible pain". Patients rated their pain by choosing a point on the scale, and the value of the point indicates the patient's VAS score. Pain rating was done before surgery, 1 week after surgery, and 1 month after surgery [16].

The postoperative recovery and recovery time were assessed 1 month after surgery according to the Knee Society Score (KSS) [17]. KSS is a 100-points scoring system for the pain, alignment, and stability of knee: ≥85 points indicated excellent conditions, 70-84 points indicated good conditions, 60-69 points indicated fair conditions, and <60 points indicated poor conditions. Total effective rate = (excellent + good)/total number of cases × 100%.

Secondary outcome measures

Follow-up indicators: The MOS item short-form health survey (SF-36 questionnaire) assessed the quality of life of patients from 8 items: general health (GH), mental health (MH), physical functioning (PF), role-physical (RP), social functioning (SF), role-emotional (RE), bodily pain (BP), and vitality (VT). Each item was scored on a 1 to 100 range. A higher score indicated a better quality of life.

Statistical analysis

Statistical analysis was performed on the SPSS 17.0 software. The continuous variables that were consistent with normal distribution and homogeneity of variance were expressed as mean ± standard deviation (X ± SD). The paired t-test was used for the intragroup comparison between before and after treatment. The independent sample t-test was used for intergroup comparison, denoted by t. Count data were expressed as % and its comparison was analyzed by the Pearson chi-square test or Fisher's exact test, denoted by the chi-square. The difference was statistically significant if $P<0.05$.

Results

General and baseline information

All patients completed the study. The two groups were not significantly different in age, sex ratio, disease type, and each item of the quality of life scale ($P>0.05$). More details are shown in **Table 1**.

Serum expression of IL-6, TNF-α, VCAM-1, and MMP-9 before and after treatment in the two groups

The comparison of the levels of IL-6, TNF-α, VCAM-1, and MMP-9 between the two groups before treatment showed no statistical differences ($P>0.05$). The expression levels of IL-6, TNF-α, VCAM-1, and MMP-9 in the two groups were markedly reduced one month after treatment compared with those before treatment ($P<0.05$), and the reductions were greater in OG than those in CG, with a statistical difference between the two groups in the levels of IL-6, TNF-α, VCAM-1, and MMP-9 after treatment ($P<0.05$). More details are shown in **Table 2** and **Figure 1**.

Scores of pain and swelling in two groups 2 weeks after surgery

The two groups were not statistically different in the scores of pain and swelling before treatment ($P>0.05$). The scores of pain and swelling in the two groups were markedly reduced after treatment compared with those before treat-

Table 1. Comparison of general and baseline data between two groups of patients

Program		Observation group (n=55)	Control group (n=55)	χ^2/t	P
Sex ratio (male: female)		34:21:00	33:22:00	0.038	0.845
Age (years)		64.2±5.5	63.8±5.7	0.532	0.596
(K-l) classification					
IV		9	12	0.53	0.476
V		46	43		
BMI (kg/m^2)		25.23±3.23	25.63±3.47	0.582	0.432
Surgery site (left: right)		32:23:00	30:25:00	0.148	0.701
Course of disease (year)		8.9±2.8	8.7±3.0	0.782	0.378
Operation time (min)		96.92±29.20	94.25±30.87	0.823	0.203
Intraoperative blood loss (ml)		150.28±39.43	152.02±40.28	0.502	0.467
Combined disease		-	-	-	-
Hyperlipidemia	have	32	30	0.135	0.714
	none	23	25		
Hypertension	have	38	32	1.269	0.26
	none	17	23		
Coronary heart disease	have	18	21	0.574	0.449
	none	37	34		
Obesity	have	18	24		
	none	37	31	1.269	0.26
Hyperhomocysteinemia	have	13	11		
	none	42	44	0.745	0.388
Hyperuricemia	have	20	16	1.386	0.239
	none	35	39		

Table 2. Serum expression of IL-6, TNF-α, VCAM-1, and MMP-9 before and after treatment in the two groups

Program	IL-6 (ug/ml)	TNF-α (ug/ml)	VCAM-1 (ng/ml)	MMP-9 (ng/ml)
Observation group before treatment	351.37±37.86	124.51±18.22	257.67±34.55	258.88±76.02
Control group before treatment	351.00±37.32	123.80±17.87	258.64±35.13	259.80±77.28
T	0.038	0.154	0.863	0.917
P	0.969	0.878	0.439	0.363
Observation group after treatment	273.27±25.64#	85.01±15.90#	211.64±29.02#	201.61±63.84#
Control group after treatment	318.34±29.73#	102.66±16.12#	233.29±28.25#	239.23±62.16#
T	6.287	4.269	6.89	7.153
P	<0.001	<0.001	<0.001	<0.001

Note: # is statistically different after treatment in the same group compared to that before treatment, P<0.05. IL: interleukin-6: TNF-α: tumor necrosis factor-α; VCAM-1: vascular cell adhesion molecule-1; MMP-9: matrix metalloproteinase-9.

ment (P<0.05), and the reductions were greater in OG than in CG, with a statistical difference between the two groups in the scores of pain and swelling after treatment (P<0.05). More details are shown in **Tables 3**-**5**.

VAS scores before and after surgery in the two groups

The two groups were not statistically different in the VAS scores before treatment (P>0.05). The VAS scores in the two groups were markedly reduced 1 week after surgery compared with those before surgery (P<0.05), and the reductions were greater in OG than in CG (P<0.05). The VAS scores in the two groups were markedly reduced 1 month after surgery compared with those 1 week after surgery and those before surgery, and the reductions were greater in OG than those in CG (P<0.05). More details are shown in **Table 6**.

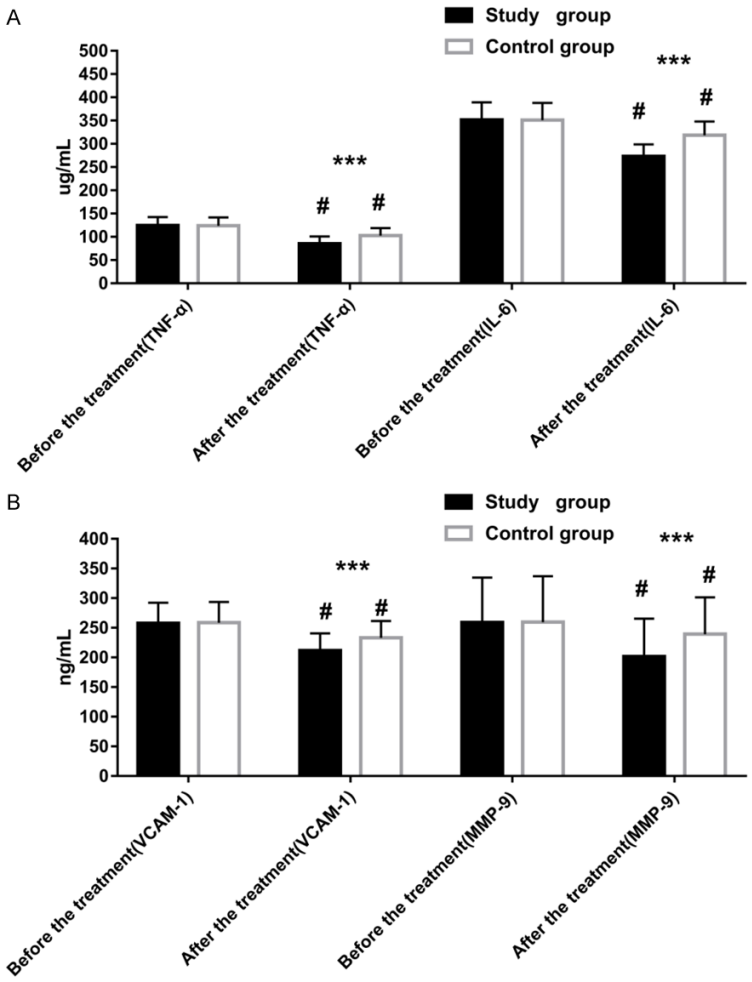

Figure 1. A shows the comparison of serum IL-6 and TNF-α in the two groups after treatment; B shows the comparison of serum VCAM-1 and MMP-9 in the two groups after treatment. * is P<0.001; # is comparison with before treatment P<0.05. IL: interleukin-6: TNF-α: tumor necrosis factor-α; VCAM-1: vascular cell adhesion molecule-1; MMP-9: matrix metalloproteinase-9.

Total effective rate in the KSS in the two groups

The total effective rate in the KSS was statistically higher in OG than that in CG (P<0.05). More details are shown in **Table 7**.

Quality of life of patients one month after surgery in the two groups

The scores of PF, RP, SF, RE, and BP one month after surgery were markedly higher in OG than in CG (P<0.05). The comparison of GH, MH, and VT between the two groups showed no statistical difference (P>0.05). The scores of PF, RP, SF, RE, and BP in the two groups were markedly higher one month after surgery compared with those before surgery (P<0.05). More details are shown in **Table 8**.

Discussion

The efficacy of total knee arthroplasty in the treatment of knee osteoarthritis has been clinically confirmed and praised [18]. Minimally invasive technology in total knee arthroplasty reduces the surgical wounds and facilitates the recovery [19]. However, about 20% of patients have a poor postoperative recovery, with only small improvements in postoperative pain, bleeding, and joint mobility [20]. So the postoperative treatment and nursing of patients are extraordinarily essential. Yunnan Baiyao is a Chinese traditional compound preparation including Panax notoginseng, Rhizoma paridis, Musk, and Radix aconiti kusnezoffii. It can promote blood circulation, remove blood stasis, relieve pain, and stop bleeding. Many studies have shown that the use of traditional Chinese medicine in animal experiments causes changes in animal blood. Yunnan Baiyao can significantly improve the hemorheology and coagulation function of animal blood and disperse blood stasis [21, 22]. Panax notoginseng, with various active ingredients, can facilitate blood circulation and stop bleeding, as well as promote bone cell activation [23-25]. Rhizoma paridis can be used for pain eliminating, anti-inflammatory, stasis removal, and anti-tumor [26]. Musk can promote bone repair and stimulate blood circulation [27]. Radix aconiti kusnezoffii can be used for analgesia, inflammation diminishing, blood circulation activation, and blood stasis removal [28]. In this study, the use of Yunnan Baiyao after surgery promoted the dissipation of stasis and swelling, and greatly relieved the physical pain, stimulating the postoperative recovery of patients, which is consistent with its pharmacological effects.

Table 3. Comparison of pain ratings between two groups of patients

Program	Grade 0	Grade 1	Grade 2	Grade 3
Pain				
Observation group before surgery	0	2	14	39
Control group before surgery	0	3	15	37
χ^2		0.287		
P		0.866		
Pain				
Observation group after surgery	11	26	12	6
Control group after surgery	3	12	23	17
χ^2		18.447		
P		<0.001		

Table 4. Comparison of swelling ratings between two groups of patients

Program	Grade 0	Grade 1	Grade 2	Grade 3
Swelling				
Observation group before surgery	0	12	12	31
Control group before surgery	0	14	13	28
χ^2		0.346		
P		0.841		
Swelling				
Observation group after surgery	13	25	7	10
Control group after surgery	5	18	10	22
χ^2		9.725		
P		0.027		

Table 5. Comparison of pain and swelling between two groups of patients before and after treatment

Program	Pain	Swelling
Observation group before treatment	5.30±1.16	4.50±1.34
Control group before treatment	5.24±1.09	4.59±1.24
T	0.221	0.154
P	0.826	0.878
Observation group after treatment	1.54±1.42#	1.57±1.42#
Control group after treatment	2.25±1.30#	2.75±1.26#
T	2.201	3.870
P	0.031	<0.001

Note: #Comparison using paired t test before and after treatment in the same group, P<0.05.

IL-6, an inflammatory cytokine, has an increased expression in early stages of knee arthritis, which triggers the degradation of cartilage matrix, damages the synovium, and induces the onset of knee arthritis [29, 30]. IL-6 can mediate the production of other inflammatory cytokines such as C-reactive protein [31]. TNF-α is a common pro-inflammatory factor like IL-6. Its serum level is positively correlated with the severity of knee osteoarthritis and can be used as an effective indicator of disease monitoring [32]. VCAM-1 induces the aggregation of leukocytes at the synovium of joints and leads to inflammatory responses [33]. MMP-9 allows leukocytes and lymph to join the blood circulation [34]. MMP-9 level rises with the increase of osteoclasts, so it can well reflect bone resorption and reconstruction [35]. Yunnan Baiyao can inhibit the release of mediators, lower capillary permeability, suppress leukocyte migration and connective tissue proliferation during the inflammation. Besides, it can inhibit staphylococcus aureus, E. coli, and pseudomonas aeruginosa. Also, Yunnan Baiyao shows marked effectiveness in relieving inflammation in animal models caused by adjuvants, carrageenan, heterologous proteins, chemical inflammatory agents, cotton ball granuloma and other inflammatory cytokines [36]. In this study, patients from OG saw a more sharp reduction in the serum levels of IL-6, TNF-α, VCAM-1 and MMP-9 after total knee arthroplasty than patients from CG. The larger decrease in OG was a result of the clearance of inflammatory sites after surgery and the anti-inflammatory and analgesic effects of Yunnan Baiyao.

Advancements in science and technology have changed the medical concept of patients. The idea of "Treatment of hidden diseases" (intervention before the occurrence of the disease) is attracting more and more attention. SF-36 questionnaire is the most preferred scale to

Table 6. VAS scores before and after surgery in the two groups

Program	Observation group (n=55)	Control group (n=55)	T	P
VAS before surgery	6.76±1.50	7.11±1.10	1.001	0.321
1 week after VAS	4.59±0.78*	5.18±0.77*	2.880	0.006
1 month after VAS	1.93±0.65*,#	2.29±0.66*,#	2.045	0.046
Difference between 1 week after VAS and preoperative	2.27±0.79	1.92±0.55	2.145	0.034
Difference between 1 month and 1 week after VAS	2.88±0.32	2.67±0.48	2.043	0.043

Note: *Comparison with VAS before surgery, *P<0.05; #Comparison with 1 week after VAS, # is P<0.05.

Table 7. Total effective rate in the KSS in the two groups

Group	Observation group	Control group	χ^2	P
Excellent	39	21	13.800	0.003
Good	12	18		
Moderate	3	12		
Poor	1	4		
Total effective rate	92.28%	70.91%	8.800	0.003

Table 8. Comparison of quality of life between the two groups of patients before and after surgery

Program	Observation group before treatment	Control group before treatment	T	P	Observation group after treatment	Control group after treatment	T	P
Health Status (GH)	73.95±3.27	74.38±3.06	0.592	0.556	75.10±3.28	75.19±3.29	0.119	0.906
Mental Health (MH)	89.05±2.87	89.05±2.84	0.006	0.995	91.50±3.34	90.22±2.85	1.084	0.75
Physiological Function (PF)	70.32±5.35	71.00±5.75	0.534	0.595	90.05±2.81***	74.19±3.17*	23.203	<0.001
Physiological Function (RP)	60.32±6.20	60.30±6.10	0.02	0.984	76.73±6.46***	65.85±6.15**	7.764	<0.001
Social Function (SF)	68.32±3.35	68.08±3.33	0.32	0.75	85.35±5.46***	73.35±5.46**	9.627	<0.001
Emotional Function (RE)	60.48±9.65	60.84±9.95	0.162	0.871	79.65±6.22***	66.81±9.87**	6.878	<0.001
Physical pain (BP)	34.12±4.28	34.22±4.18	0.095	0.925	37.18±4.03*	32.14±4.28	5.139	<0.001
Energy (VT)	85.05±2.87	80.05±2.84	0.006	0.995	91.50±3.34	90.22±2.85	1.804	0.75

Note: *Comparison of patients in the same group 1 month after surgery and before surgery, where * is P<0.05, ** is P<0.01, and *** is P<0.001.

assess the quality of life of patients clinically [37]. In this study, the two groups were statistically different in the scores of PF, RP, SF, RE, and BP two months after surgery, but with no marked difference in GH, MH, and VT. Patients from OG had a quick postoperative recovery of knee joint activity. Patients from CG suffered from a long time of pain and swelling of the joint and had a slower recovery and limited knee joint activities, facing certain impacts on their physical, psychological, and social functions. We should strengthen the postoperative guidance to eliminate the patient's physical and psychological barriers [38].

The sample size of this study is small and the follow-up time is short. We should include more samples and increase the follow-up time to explore the long-term effects of the two treatment methods on the quality of life of patients.

In summary, total knee arthroplasty combined with Yunnan Baiyao showed marked efficacy in the treatment of knee osteoarthritis. This combined therapy can relieve the pain and swelling, promote the clearance of inflammatory cytokines, and enhance the postoperative quality of life of patients, thus it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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