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ORIGINAL ARTICLE

Herbal Fufang Xian Ling Gu Bao prevents corticosteroid-induced osteonecrosis of the femoral head—A first multicentre, randomised, double-blind, placebo-controlled clinical trial

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KEYWORDS
Clinical trial;
Corticosteroid;
Osteonecrosis

Abstract *Background/Objective:* This is a multicentre, randomised, double-blind, placebo-controlled clinical trial to investigate the safety and efficacy of Chinese herbal Fufang Xian Ling Gu Bao (XLGB) with antiadipogenic compounds for the prevention of corticosteroid (CS)-induced osteonecrosis of femoral head (ONFH).
Methods: Patients of both genders, aged between 18 and 65 years, with diseases such as systemic lupus erythematosus, nephrosis, dermatosis and rheumatoid arthritis indicated for CS treatment and who did not show magnetic resonance imaging of ONFH at baseline were recruited into the study and then randomised into either XLGB group (n = 129) with daily oral administration of XLGB or placebo group (n = 146).
Results: Magnetic resonance imaging revealed a total of 30 ONFH cases at 6 months after CS treatment, with 6.98% (9 of 129 cases) and 14.4% (21 of 146 cases) in the XLGB group and placebo group, respectively, ($p < 0.05$), i.e., a 2-fold significantly less ONFH identified in the XLGB treatment group. Blood tests suggested that XLGB significantly inhibited the elevation of activated protein C resistance induced by CS treatment.
Conclusion: This is the first multicentre clinical study to demonstrate that the antiadipogenic compounds—rich herbal Fufang (formula) XLGB is effective in preventing CS-associated ONFH in patients with immune-inflammatory diseases under CS treatment.
The translational potential of this article: The translation potential of this clinical trial is that the initially officially approved clinical indication for XLGB for treatment of osteoporosis has been now also proven to be effective for a new clinical application.

Introduction

Corticosteroids (CSs) are indicated for treatment of many metabolic disorders. However, high-dose and/or long-term use of CS can induce osteonecrosis [1]. Femoral head is the skeletal site with the highest incidence of osteonecrosis and leads to significant impairment of the joint functions. Clinical data show that there is a high risk of osteonecrosis of the femoral head (ONFH) when the accumulated CS dosage reaches 2,000 mg (converted into methylprednisolone, similarly hereinafter) or average daily dosage is above 30 mg, especially in patients receiving a high dose of CS in the first 2 weeks of treatment. The ONFH incidence was reported to be 0.7—33% [2]. Another study reported that high dose of CS therapy for systemic lupus erythematosus induced 44% of osteonecrosis predominantly in the hips and knees [3]. Furthermore, if no preventive treatments were given to patients with osteonecrosis, almost 80% of them would suffer hip joint collapse in the first 1—5 years [4,5]. Once the hip joint starts to collapse, most joints would develop osteoarthritis, and some would eventually require total hip replacements [6]. Nonoperative treatments and surgical interventions for patients with osteonecrosis could postpone the timing of hip replacements. It is therefore highly desirable to establish a preventive strategy to avoid CS-induced ONFH.

The underlying mechanism of CS-induced ONFH is still unclear, although many research focused on the pathophysiological mechanisms and revealed that apoptosis of osteocytes and osteoblasts, oxidative stress, bone marrow endothelial cells damage, hypercoagulability and low fibrinolysis state, microRNA demethylation [7] and uncontrolled vascular endothelial growth factor (VEGF) signalling pathway could contribute to CS-induced ONFH [1,8]. In addition, a comprehensive study of glucocorticoid-induced osteonecrosis had identified that glutamate receptor gene variants would be a risk factor of ONFH [9].

It has been confirmed that more than 90% of CS-induced ONFH cases can be diagnosed by typical magnetic resonance imaging (MRI) within the first 24 weeks from being treated with CS [9]. Several preclinical proof-of-concept studies tested therapies for prevention and treatment of osteonecrosis using animal models with similar pathophysiological mechanisms [10,11]. Anticoagulant, lipid-lowering agents and Traditional Chinese Medicine (TCM)—derived herbs or compounds have been tested preclinically for their efficacy in preventing steroid-induced osteonecrosis in rats [12] and in rabbits [13—15]. Besides, a study reported that statin therapy could reduce the risk of osteonecrosis in patients receiving steroids over an average of 7.5 years [16]. It has also been reported that an anticoagulant, warfarin, prevented steroid-induced ONFH in systemic lupus erythematosus [17]. Furthermore, an immunosuppressive agent, tacrolimus, might be associated with the lower rate of osteonecrosis after renal transplantations [18] although a recent study reported enthusiasm for statins and anticoagulants as preventive agents yet without clear long-term clinical therapeutic benefits [19].

Xian Ling Gu Bao (XLGB) Fufang is an herbal formula encapsulated for oral administration, which has been approved by the China Food and Drug Administration (China, Z20025337). It has been clinically used for the treatment of postmenopausal osteoporosis over past 20 years. Recently, well-designed single-centre and multicentre clinical trials demonstrated their clinical efficacy and safety [15,20]. As CS impairs osteogenesis of osteoblasts and increases apoptosis of osteoblasts and osteocytes

and the adipogenic potential of bone marrow mesenchymal cells, Fufang herbs may share the common pathways or the similar underlying mechanisms for the prevention of both osteoporosis and osteonecrosis [21]. Moreover, around 90% of the patients with CS-induced osteonecrosis coexisted with or accompanied by osteoporosis [22].

Although XLGB is currently recommended for the prevention of CS-induced osteonecrosis in China [23], it lacks multicentre clinical trials to prove its efficacy. The aim of the present study is therefore to assess the safety and preventive efficacy of XLGB in CS-induced ONFH in a multicentre, randomised, double-blind, placebo-controlled prospective clinical trial.

Methods

Ethics statement

This study was officially registered, and all experimental protocols were approved by the International Clinical Trial Registration (Supplement I), together with Human ethics approval (Supplement II). All experiments were performed in accordance with the approved guidelines and regulations, with informed consent obtained from all patients.

Patients and study design

This study was a multicentre, randomised, double-blind, placebo-controlled clinical trial carried out to assess the safety and efficacy of XLGB in preventing CS-induced ONFH. Inclusion criteria were as follows: Patients of both genders, aged between 18 and 65 years and indicated for CS therapy yet without MRI of ONFH at baseline were recruited from six clinical sites, including those with autoimmune diseases, nephrosis, systemic lupus erythematosus and immune-inflammatory diseases [24]. The CS therapies consisted of an average daily dose $\geq$30 mg, medication duration $\geq$30 days, total dose $\geq$2000 mg or intravenous prednisone pulse therapy $\geq$800 mg/day continued for 3 or more days. The exclusion criteria were pregnant and lactating women, patients with drug allergies, severe cardiovascular diseases, liver and kidney dysfunction, haematopoietic system diseases, mental diseases and/or patients who are not suitable for MRI examination (claustrophobic, with cardiac pacemakers or with metallic foreign object in the body).

Patients were excluded if they did not meet the inclusion criteria or could not comply with the study protocol or with primary disease aggravated that they could not continue with the trial. Informed consent was obtained from all patients.

Daily dose of methylprednisolone tablets were administrated orally for CS treatment, and methylprednisolone sodium succinate was used for the intravenous pulse therapy.

All eligible patients were assigned to XLGB treatment group or placebo control group via computer-generated randomisation. Patients from both groups took four capsules each time and twice daily. The placebo (calcium) capsule was in the same shape and colour as the XLGB capsule. All patients and clinical staff were blinded to the group assignment until encoding for data analysis.

Before the study, MRI of bilateral hips (1.5T, GE Medical Systems, Milwaukee WI, USA) was performed using the following two settings, coronal T1WI (TR 400 ms/TE 8.6 ms/Ef, 4 mm thickness, 0.3 mm gap, 34 $\times$ 34 cm field of view, 256 $\times$ 192 matrix and excitation) and fat-suppressed T2 (TR 2560 ms/TE 108 ms) or Short Tau (t) (inversion time) Inversion Recovery (STIR). Patients with no osteonecrosis found on MRI were enrolled. At 24 weeks after receiving CS treatment, a second MRI scan was conducted to confirm the occurrence of osteonecrosis at bilateral hips according to the Association Research Circulation Osseous Standard [25].

Magnetic resonance imaging evaluation of osteonecrosis as primary study outcome

MRI images were evaluated by qualified musculoskeletal radiologists. Radiologists were blinded to the grouping. At baseline, no ONFH was observed in the MRI images of all patients as this was set as inclusion criteria. At 24 weeks after CS treatment, MRI scanning was taken for the diagnosis of ONFH.

Safety evaluations

The frequency of follow-up visits was once every 6 weeks. Adverse events were recorded during the trial period, including obvious drug rashes and clinical symptoms, liver and kidney dysfunction, obvious clotting disorders and myocardial toxicity. Patients with severe adverse events were excluded from further study.

Blood tests

For testing blood coagulation, blood samples were collected from 13 patients of the XLGB group and 17 patients of the placebo group from one clinical site. Activated protein C resistance (APCR) was measured using an APCR kit (Staclot APC-R; Diagnostica Stago, Asnieres, France, Cat. No.00721). Antithrombin III (ATIII) levels were determined using the Stachrom ATIII chromogenic assay (Diagnostica Stago, Cat. No.05067). Plasminogen activator inhibitor-1 (PAI-1) was measured using Human PAI-1 ELISA Kit (China, IB-11067).

Statistical analysis

Based on the previous study on incidence of CS-associated osteonecrosis (ON) [2,5,26], we estimated a 20% of CS-associated ON at one skeletal site at least, and the treatment should be able to reduce half of ON incidence. This ended up with 199 patients in each arm of the study groups (CS control group vs. XLGB-treated CS group) to reach 0.05 statistical significance level with a statistical power of 0.8. All quantitative data were expressed as mean $\pm$ standard deviation. Chi-square test was used to detect potential differences in ONFH incidence and/or incidence of severe adverse events between the XLGB group and placebo group. Two-factor repeated-measures analysis of variance was used to test if there were changes in blood coagulation indices between baseline and at 24 weeks and between XLGB group and placebo group. Paired sample *t* test was

used to compare the change of blood coagulation indices between baseline and at 24 weeks within the XLGB group or placebo group. Mann—Whitney test was used to compare the differences in blood indices between the XLGB and placebo group. Statistical analysis was performed using SPSS 17.0 software (Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

Results

Baseline data

Patients were recruited from six China Food and Drug Administration—certified clinical centres in China. A total of 419 patients were initially identified, who met the inclusion criteria, and were then indicated for CS treatment. There was a total of 34% dropout during the study period. A total of 275 patients, including 129 cases from the XLGB group and 146 cases from the placebo control group, completed the study and were compared statistically (Fig. 1).

Statistical analysis showed that there were no differences in gender, age, primary diseases, total dosage of CS administration, average daily dosage or duration of CS treatment between the XLGB group and placebo control group (Table 1).

Osteonecrosis of femoral head

A total of 30 ONFH cases (24 bilateral and 6 unilateral) among all patients were identified from the MRIs at 24 weeks after CS treatment. There was no significant difference in gender and age between patients identified with ONFH in both groups (11 males and 19 females, age between 20 and 51 years). In the placebo control group, 14.4% ONFH incidence (21 ONFH cases, 19 bilateral and 2 unilateral) was identified, i.e., twofold significantly higher than 6.98% ONFH in the XLGB treatment group (9 ONFH cases, 5 bilateral and 4 unilateral) ($p < 0.05$) (Fig. 2 and Table 2).

Safety

No patients died during the study period. No statistical difference in interventional safety was found between the two groups at follow-up. On the first follow-up visit at week 6, seven patients reported rashes and erythema on skin of face, hand and foot, including four in the XLGB group and three in the placebo control group. The symptoms were subsided by local drug treatment. On the second follow-up visit at week 12, oedema in the lower extremity was found in one patient in the placebo control group, and symptom was relieved after treatment. On the third follow-up visit at week 18, electrocardiographic abnormality was found in 22 cases, including 10 in the XLGB group and 12 in the placebo control group, yet with no statistical differences between groups. Symptoms were relieved after treatment. All aforementioned cases were not withdrawn from the study and were used for statistical analysis. On the fourth follow-up visit at week 24, leucocytosis and elevated liver transaminase levels were observed in 66 cases, including 31 in the XLGB group and 35 in the placebo control group from the routine blood tests, yet with no significant difference between groups. The number of white blood cells and liver transaminase levels were within normal range after treatment, and no patient was withdrawn from the study. In the XLGB group, a patient with nephrotic syndrome reported

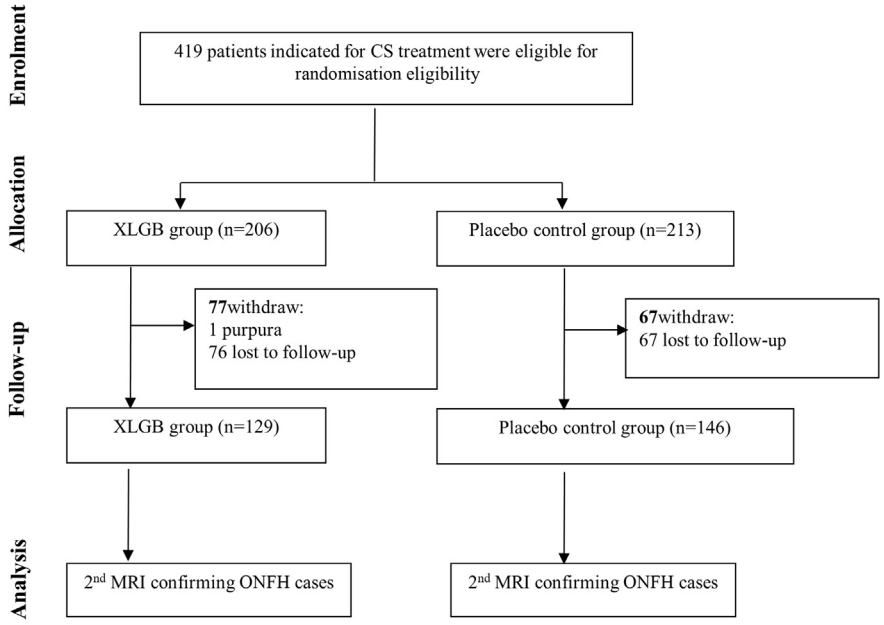

Figure 1 Patients recruitment and randomisation: 419 patients indicated for receiving CS treatment were enrolled into the study. After eliminating those who did not complete the study or had not attended second MRI scanning 24 weeks after CS treatment (144 cases), 275 cases completed the follow-up study for evaluation and statistical analysis, including 129 cases in the XLGB administration group and 146 cases in the placebo group.
CS = corticosteroid; MRI = magnetic resonance imaging; ONFH = osteonecrosis of femoral head; XLGB = Xian Ling Gu Bao.

Table 1 Basic characteristics of patients indicated for corticosteroid administration.

Items	XLGB group (n = 129)	Placebo group (n = 146)	p
Gender			0.5416
Male	38	48	
Female	91	98	
Total	129	146	
Age (y)			0.9998
20—29	41	47	
30—39	28	31	
40—49	29	32	
50—59	26	30	
60—65	5	6	
Total	129	146	
Primary diseases			0.3857
Systemic lupus erythematosus	19	18	
Nephrosis	60	62	
Dermatosis	14	13	
Rheumatoid arthritis	21	23	
Others	15	30	
Total	129	146	
Total CS usage (mg)			0.8184
>5000	22	22	
3000—4999	59	72	
2000—3999	48	52	
Total	129	146	
Daily CS usage (mg, on average)			0.4419
>50	21	29	
30—49	108	117	
Total	129	146	
Duration of CS treatment [d, on average (range)]	92 (36—152)	95 (36—150)	0.6521

CS = corticosteroid; XLGB = Xian Ling Gu Bao.

Table 2 Between-group comparison for incidence of ONFH.

Cases	XLBG group (n = 129)	Placebo group (n = 146)	p
ONFH	9 (6.98%)	21 (14.4%)	0.0493*
Bilateral	5	19	
Unilateral	4	2	

ONFH = osteonecrosis of femoral head; XLGB = Xian Ling Gu Bao. *: $p < 0.05$, Chi-square test.

purpura and was treated, but was withdrawn from the study. Chi-square analysis showed that there was no statistical difference in the incidence of severe adverse events between groups (Table 3).

Blood coagulation indices

Paired t test showed that both the APCR and ATIII levels were significantly increased by 21.1% ($p < 0.05$) and 13.8% ($p < 0.05$), respectively, at week 24 after CS treatment when compared with the baseline in the placebo group; whereas in the XLGB group, the APCR and ATIII levels did not show significant changes 24 weeks after CS treatment. Repeated-measures analysis of variance showed that daily oral administration of herbal Fufang XLGB could significantly prevent the increase of APCR induced by CS treatment ($p < 0.05$). However, there was no between-group or temporal difference found in plasminogen activator inhibitor-1 (Table 4).

Discussion

This was the first prospective, multicentre, double-blind, randomised, placebo-controlled clinical trial of a traditional bone-protective herbal Fufang XLGB for the prevention of CS-

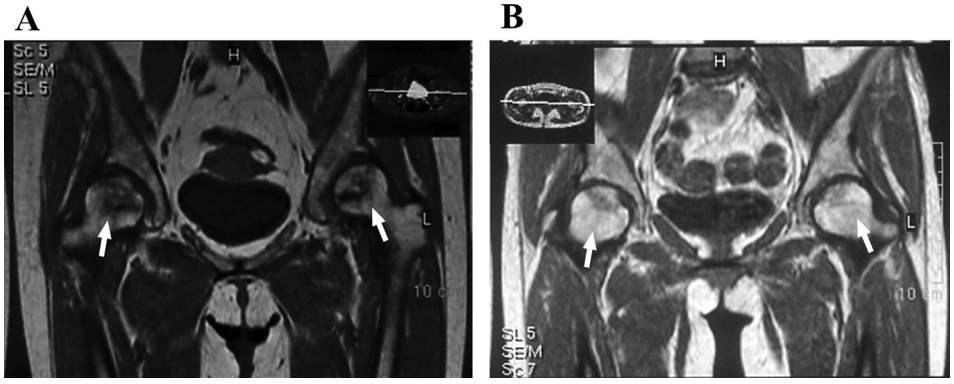

Figure 2 (A) CS-induced ONFH from the placebo group: bilateral femoral head necrosis with large necrotic area (white arrow). Female, 46 years old, nephritis, accumulate 4,500 mg (30 mg daily for 150 days) CSs. (B) CS-induced ONFH from the XLGB group: right femoral head necrosis with small necrotic area (white arrow). Female, 21 years old, chronic nephritis, accumulate 4,350 mg (30 mg daily for 145 days) CSs.
CS = corticosteroid; ONFH = osteonecrosis of femoral head; XLGB = Xian Ling Gu Bao.

Table 3 Safety evaluations.

Cases	XLBG group ($n = 21$)				Placebo group ($n = 14$)			
	6 weeks	12 weeks	18 weeks	24 weeks	6 weeks	12 weeks	18 weeks	24 weeks
Rashes and erythema at skin of face, hand and foot	4	0	0	0	3	0	0	0
Oedema of lower extremity	0	0	0	0	0	1	0	0
Electrocardiographic abnormality	0	0	10	0	0	0	12	0
Abnormity in routine laboratory examination (including leucocytosis and elevated liver transaminase levels)	0	0	0	31	0	0	0	35

XLGB = Xian Ling Gu Bao.
Chi-square analysis showed no statistical difference in the incidence of severe adverse events between groups ($p > 0.05$ for all events).

Table 4 Blood chemistry analysis.

Blood coagulation indices	XLGB group ($n = 13$)		Placebo group ($n = 17$)	
	Baseline	24 weeks	Baseline	24 weeks
APCR levels (Sec)	224.5 ± 66.4	184.9 ± 73.1[#]	182.2 ± 73.1	220.6 ± 62.1*
ATIII (%)	98.5 ± 18.5	103.5 ± 18.4	99.6 ± 23.4	113.3 ± 21.6*
API-1 (mg/L)	2.01 ± 2.76	1.83 ± 3.12	2.00 ± 2.02	1.99 ± 1.79

APCR = activated protein C resistance; ATIII = antithrombin III; API-1 = plasminogen activator inhibitor-1; XLGB = Xian Ling Gu Bao. Data are given as mean ± standard deviation. *: $p < 0.05$ compared between 24 weeks and baseline, paired sample t test. [#]: $p < 0.05$ to test the interaction between XLGB and 24 weeks of corticosteroid (CS) treatment, repeated-measures analysis of variance.

associated ONFH. Osteonecrosis is a known side effect of CS treatment, especially at the hip, a relevant skeletal site or joint for locomotion. To study the preventive potential of herbal Fufang XLGB on osteonecrosis, patients were asked to take XLGB capsules and were compared with those without any preventive measures. The twofold significant reduction of ONFH incidence in patients who received XLGB capsules suggests that XLGB has potential to achieve better recovery or prognosis for CS-induced ONFH.

CS-induced ONFH takes a significant proportion in nontraumatic ONFH, especially in China. According to a study performed by the Sino-Japan Friendship Hospital in Beijing, China, 1,064 cases of nontraumatic ONFH were recorded, and among them, 42% were attributed by CS administration [2]. A latest multicentre epidemiologic study on 6,395 cases of ONFH in China reported 24.1% incidence of steroid-induced osteonecrosis [26]. In Taiwan, a study reported that the proportion of bilateral ONFH was higher in the CS group (72.4%) than in the alcohol (62.5%) or idiopathic groups (45.3%) [27]. According to the international consensus, CS treatment is a high risk factor for ONFH if the accumulated CS administration is more than 2,000 mg and more than 30 mg per day or with a short-term high dose of pulsed CS therapy [2]. In this study, all cases with autoimmune diseases were indicated for CS therapy, and the high CS dosage belongs to a high risk of ONFH. The international consensus also indicates that CS-induced ONFH occurs within 6 months after CS treatment, and MRI is highly specific and sensitive for the diagnosis of early osteonecrosis. The differences observed from the MRI imaging are regarded as the gold standard for ONFH diagnosis [16,17]. The parameters adopted in the evaluation protocols of this study were based on the international consensus methods [16,17].

Treatment efficacy of CS-induced ONFH and potential underlying mechanism

CS-induced ONFH is a multifactorial disorder. A consensus etiopathogenesis of steroid-associated ON has been recently unified on both intravascular thrombosis-induced occlusion and extravascular lipid deposition—induced pressure, leading to impairment of intraosseous blood supply [28]. Therefore, an ideal agent for preventing CS-induced ONFH should simultaneously target both intravascular thrombosis and extravascular lipid deposition [22]. Motomura et al combined anticoagulant and lipid-lowering treatments in animal models and showed that the combined drug group had a significantly lower incidence of osteonecrosis than both the anticoagulant and the lipid-lowering groups (5%, 33% and 38%, respectively) [13]. This finding was confirmed further by an animal study [14].

Herbal Fufang XLGB consists of six herbs with weight proportion as follows: Herba epimedii (70%), Radix Dipsaci (10%), Radix Salviae miltiorrhizae (5%), Rhizoma anemarrahenae (5%), Fructus Psoraleae (5%) and *Rehmannia glutinosa* (5%) [20]. Chemical analysis showed that there was a diverse group of compounds with different structures in this formula, such as flavonoids [29], coumarins, saponins, alkalines, sugars and terpenes [30]. Multiple compounds would be ideal in treating diseases with different pathogenesis. According to the Traditional Chinese Medicine theory, Radix salviae miltiorrhizae can "promote blood circulation and remove blood stasis," whereas Herba epimedii (*Epimedium*) can "tonify the kidney and strengthen bones", which addresses the strategy for preventing CS-induced ONFH. XLGB reduced almost 50% of osteonecrosis

occurrence in the present study, whereas the anticoagulant warfarin reduced about 36% of osteonecrosis occurrence [17]. A previous preclinical study showed that the flavonoid extract of *Epimedium*, which made 70 wt% in the XLGB capsule, successfully prevented steroid-associated osteonecrosis in rabbits [15] and ovariectomised osteoporosis in mice [31]. Furthermore, the main bioactive component icariin and its metabolite icaritin of *Epimedium* both exerted preventive effects on steroid-associated osteonecrosis in rabbits [32,33] and osteoporosis in ovariectomised rats [34]. It was reported that *Epimedium*-derived phytoestrogen and single herbal molecule icaritin decreased thrombosis and vessel leakage in bone marrow [35]. The underlying mechanism was explained by its effects on the inhibition of both intravascular thrombosis and extravascular lipid deposition via the suppression of the upregulated peroxisome proliferator-activated receptor gamma (PPARγ) expression for extravascular adipogenesis of mesenchymal stem cells and protection from activated oxidative stress for intravascular endothelium injury [15,32,33].

Effect of XLGB on inhibition of intravascular thrombosis

Endothelium injury is recognised to be an important initial contributor to intravascular thrombosis. The imbalance between coagulation and fibrinolysis may predispose intravascular thrombosis. APCR, AT-III and PAI-1 are important indicators of coagulation and fibrinolysis. APCR is a haemostatic disorder characterised by a poor anticoagulant response to activated protein C, which results in an increased risk of venous thrombosis and may lead to blockage of blood circulation, such as pulmonary embolism [36]. Our results found that APCR level was significantly increased at 24 weeks after CS treatment in the placebo control group, whereas XLGB could significantly prevent the increase of APCR induced by CS treatment. These suggest that XLGB could prevent the increased risk of thrombosis induced by CS treatment. Furthermore, our *in vitro* study confirmed that desmethylicaritin, another bioactive metabolite of XLGB, protected the human umbilical vein endothelial cells from lipopolysaccharides (LPS)-induced cell damage via deceasing thrombomodulin and promoting nitric oxide formation partially through endothelial nitric oxide synthase (eNOS)-derived nitric oxide production (Supplement III). In addition, icaritin was able to protect the intact intraosseous vascularity against intraosseous vasculature hyperpermeability [33].

Safety and compliance

XLGB is a prescription herbal medicine officially approved for the treatment of general metabolic disorders of musculoskeletal disorders in postmenopausal women in China. In the present study, we recorded adverse effects in the XLGB group and control group, including purpura, rashes, erythema, oedema of lower extremity, electrocardiographic, leucocytosis and elevated liver transaminase levels. However, there is no significant difference between the two groups in adverse effects on aggravating pathological impact on liver, kidney, heart and blood system. This was also well supported by a previous multicentre clinical trial that focused on the safety of the primary end point and systemically evaluated the concerns of adverse events on gastrointestinal, renal and liver functions. One year of daily administration of XLGB showed no significant difference in the incidence of persistent adverse events between the XLGB groups and control group [20].

Limitations

One of the limitations of this study was rather higher dropout rate. The present study documented a 31.5% dropout rate in the control group compared with 37.4% in the XLGB treatment group. The major reason was due to losing contact, a unique situation of fast relocation of families from one city to another in China, especially moving away from the cities where we conducted this multicentre clinical trial in spite of great effort to maintain the study population.

All six sites of the current clinical trial followed Association Research Circulation Osseous Standard's diagnostic criteria of ONFH by experienced radiologists [25], although we did not conduct interrater or intrarater reliability test that could be included in future large-scaled clinical trials.

We used 6 months as the study time point for comparing ONFH. Nagasawa et al found that CS-induced osteonecrosis developed in early phase, i.e., within the first 3 months in 89% patients, whereas symptomatic ONFH appeared in 1—4 years after CS treatment [17]. Therefore, more ONFH cases might be diagnosed with longer study duration [37]. Another limitation was that we used MRI to confirm the prevention efficacy, and only one centre evaluated blood chemistry that may explain potential underlying mechanisms of herbal Fufang XLGB for the prevention of CS-induced ONFH.

The XLGB capsule used in this study was marketed by Tongjitang (Guizhou) Pharmaceutical Co., Ltd. The main component *Epimedium* was refined from the plant in special planting base. It is unknown if *Epimedium* planted in other places would have the same effect [29]. In this study, the content of icariin is 0.3 g/capsule that has been the conventional dose used in our clinical practice for treatment of osteoporosis. The dosing effects remain for future clinical studies.

Conclusion

In conclusion, this is the first prospective, multicentre, randomised, double-blind placebo-controlled clinical trial that confirms the preventive effects of osteoprotective herbal Fufang XLGB on CS-induced ONFH, with the underlining mechanism at least in part that XLGB prevented CS-induced coagulation and fibrinolysis. These suggest that daily oral administration of XLGB capsules could be prescribed for patients receiving CS therapy to reduce incidence of CS-induced ONFH.

Conflicts of interest

All authors declare that they have no conflict of interest.

Acknowledgement

All XLGB capsules were provided by Sinopharm Tongjitang Pharmaceutical Company Limited (Guizhou) for this study. Institutional support of participating trial centres is appreciated.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jot.2017.11.001.

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