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Original article

Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis: a randomized, double-blind, controlled equivalence drug trial

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Abstract

Objective. To demonstrate clinical equivalence between two standardized Ayurveda (India) formulations (SGCG and SGC), glucosamine and celecoxib (NSAID).

Methods. Ayurvedic formulations (extracts of *Tinospora cordifolia*, *Zingiber officinale*, *Emblica officinalis*, *Boswellia serrata*), glucosamine sulphate (2 g daily) and celecoxib (200 mg daily) were evaluated in a randomized, double-blind, parallel-efficacy, four-arm, multicentre equivalence drug trial of 24 weeks duration. A total of 440 eligible patients suffering from symptomatic knee OA were enrolled and monitored as per protocol. Primary efficacy variables were active body weight-bearing pain (visual analogue scale) and modified WOMAC pain and functional difficulty Likert score (for knee and hip); the corresponding *a priori* equivalence ranges were ±1.5 cm, ±2.5 and ±8.5.

Results. Differences between the intervention arms for mean changes in primary efficacy variables were within the equivalence range by intent-to-treat and per protocol analysis. Twenty-six patients showed asymptomatic increased serum glutamic pyruvic transaminase (SGPT) with otherwise normal liver function; seven patients (Ayurvedic intervention) were withdrawn and SGPT normalized after stopping the drug. Other adverse events were mild and did not differ by intervention. Overall, 28% of patients withdrew from the study.

Conclusion. In this 6-month controlled study of knee OA, Ayurvedic formulations (especially SGCG) significantly reduced knee pain and improved knee function and were equivalent to glucosamine and celecoxib. The unexpected SGPT rise requires further safety assessment.

Trial registration: Clinical Drug Trial Registry - India, www.ctri.nic.in, CTRI/2008/091/000063.

Key words: arthritis, osteoarthritis, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), chondroprotective agents, Ayurvedic medicines, ethnic medicine, drug trials, equivalence drug trials, herbal drugs.

CLINICAL SCIENCE

Introduction

Therapeutic options for chronic knee OA, a ubiquitous disorder [1, 2], are grossly limited to principally providing symptomatic long-term pain relief that exposes patients to potentially serious toxicity [3]. Glucosamine is widely used to treat OA and is allegedly a chondroprotective drug, but its efficacy remains contentious [4, 5]. Eventually patients may deteriorate to end-stage arthritis requiring joint replacement surgery, which is expensive and not universally accessible.

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The ancient Ayurveda medicinal system [6, 7] is popularly practised in the Indian subcontinent. The government of India recently launched the New Millennium Indian Technology Leadership Initiative (NMITLI) programme [8] and included Ayurveda. Knee OA was chosen as a key therapeutic target to validate some potential Ayurvedic drugs. We carried out several experimental studies and drug trials. The results of the final drug trial are presented.

Patients and methods

Patient enrolment began in January 2006 and the last follow-up was completed in August 2007. This trial was carried out at the All India Institute of Medical Sciences (New Delhi), Nizam Institute of Medical Sciences (Hyderabad) and Centre for Rheumatic Diseases (CRD, Pune). The ethics committee of each site (CRD Pune, AIIMS New Delhi, KEM Hospital Mumbai and NIMS Hyderabad) approved the study. Consent was obtained from each patient in the study and patients were suitably counselled before obtaining an informed consent. Several details of the NMITLI protocol and validation approach were published previously [8].

This was a randomized, double-blind, parallel-efficacy, four-arm, multicentre non-commercial investigator-initiated drug trial of 24 weeks' duration comparing two standard Ayurvedic formulations, glucosamine and celecoxib, for equivalent effectiveness. Study evaluation visits were made at baseline and weeks 2, 4, 8, 12, 16, 20 and 24 (completion). The study was conducted in compliance with the Good Clinical Practice guidelines (ICH) and Declaration of Helsinki and national regulations.

Ayurvedic formulations

(i) Selection: based on Ayurveda texts [6, 9, 10] and expert opinion, several anti-arthritis medicinal plants were short-listed and evaluated serially in exploratory clinical trials [8, 11] and experimental studies [12, 13]. Two shunthi-guduchi formulations (SGC and SGCG), each containing amalaki (*Emblica officinalis*), were identified for the current trial; in addition SGCG contained guggul (*Boswellia serrata*).

(ii) Test materials: after authentication by the National Institute of Science Communication and Information Resources (NISCAIR, New Delhi), all voucher samples (botanical materials) were deposited in the official herbarium (Agharkar Research Institute, Pune). Quality-certified standard generic forms of glucosamine sulphate and celecoxib were procured from a government (India)-accredited company (Natural Remedies, Bangalore, India).

(iii) Standardization and manufacture: traditional procedures [10] were used to extract plant material. At least one phytochemical reference marker (e.g. boswellic acid for *B. serrata*) was used to standardize each plant extract; other standard checks included assays for microbial load, heavy metals, pesticide residues and aflatoxins.

The total quantity of Ayurvedic formulations required for the trial was manufactured in a single batch. The detail ingredients of SGCG and SGC are shown in supplementary Table 1, available at *Rheumatology* Online. Each SGCG capsule (400 mg) contained *Zingiber officinale*, *Tinospora cordifolia*, *Phyllanthus emblica* and *B. serrata*. The SGC capsule (400 mg) was similar to SGCG (both for content and quantity) except for the absence of *B. serrata* extract and a higher quantity of excipients. The intervention study drug capsules were similar for physical appearance, size, taste and smell.

(iv) Safety and activity: Standard animal (mice) toxicity studies carried out as per current OECD guidelines [14] confirmed safety.

Patient selection

Patients with chronic knee pain (Fig. 1) were screened in outpatient clinics and cost-free community arthritis camps as described elsewhere [15].

Inclusion criteria

Patients of either sex in the age range 40–70 years with a diagnosis of knee OA as per modified ACR classification [16] criteria (the lower age limit was 40 years) and pain visual analogue scale (VAS) score $\geqslant 4$ cm in one or both knees while performing a weight-bearing activity (e.g. walking, standing, climbing staircase) during the preceding 24 hours were included in the study; ambulant patients required frequent analgesics.

Exclusion criteria (major)

Pregnant or lactating women or women with childbearing potential and not following adequate contraception; patients with non-degenerative joint disorders, severe disabling arthritis (including wheelchair bound) or a history of spine and lower limb surgery; patients on medication likely to influence efficacy evaluation (except paracetamol rescue); patients with a history of peptic ulcer bleed or recent active peptic ulcer and patients with any unstable severe medical disease were excluded.

Randomization

Patients were screened and randomized on a first-come, first-served basis. The study biostatistician (S.S.) used a standard software program to generate a randomized schedule of permuted block randomization with block size 4 for blinded (coded) drug allotment.

Washout period

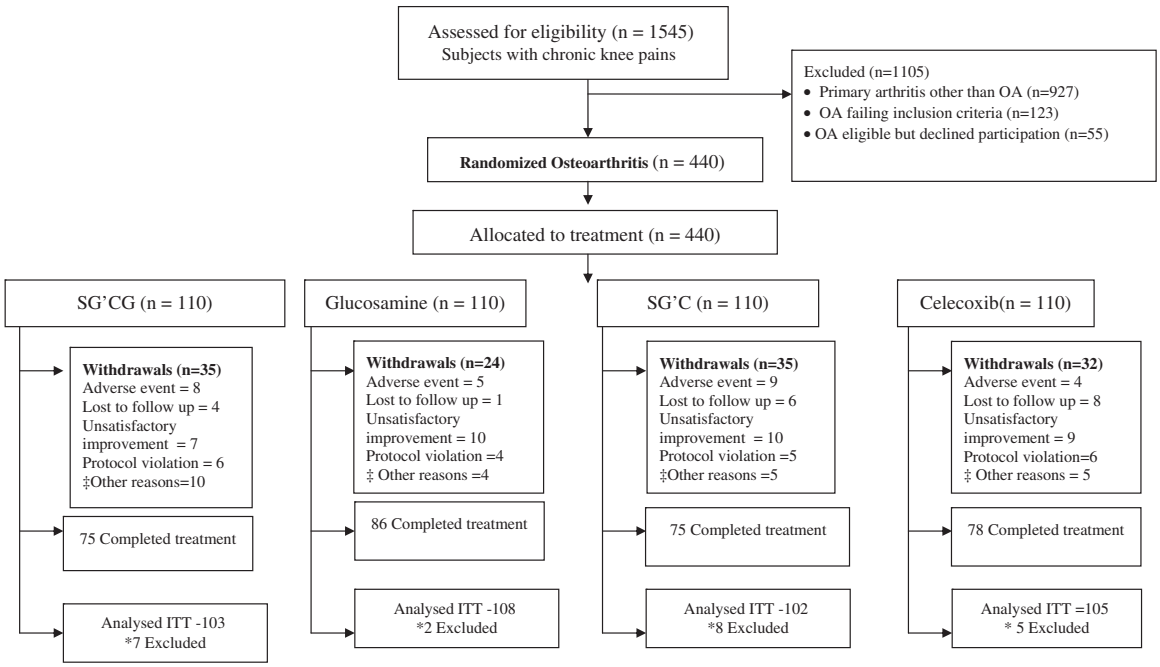
All patients taking NSAID analgesics prior to randomization underwent a washout period of 2–5 days.

Main outcome measures

Clinical evaluation

Active pain and WOMAC (version LK3) [17–19] pain score and functional difficulty score were the primary efficacy variables and were recorded at every visit. Maximum active pain on body weight-bearing activity (e.g. walking)

Fig. 1 Flow of patients.



‡Other reasons include noncompliance and migration of patient to distant location. *Patients did not report for follow-up after randomization.

during the preceding 24 hours was recorded for each knee on a horizontal 10 cm VAS (anchored at 0 for absent pain and 10 for maximum pain). A validated modified version of the WOMAC questionnaire [20] suitable for Indian patients and available in several Indian languages was used. Patients provided categorical answers for scoring (none = 0, mild = 1, moderate = 2, severe = 3, extreme = 4) and the maximum score (of 24 questions) was 96. Several secondary efficacy variables (clinical and laboratory) included pain VAS on rest and physician and patient global assessment (grades 1–5 corresponding to asymptomatic to very severe).

Intervention

The dose regimen for all study intervention drugs was two capsules three times a day taken with plain water after a meal or snack. Oral glucosamine sulphate (2 g daily) and celecoxib (200 mg daily) were administered in a similar manner (three times a day in equally divided doses).

A fixed quantity of paracetamol (500 mg tablet) was provided for emergency analgesic use. Ongoing concomitant medication for concurrent chronic illnesses was permitted. Patients were not allowed treatment with any other alternative medicinal system (such as homeopathy, acupuncture or acupressure). Patients could continue their regular exercise and/or physiotherapy programme begun prior to the current trial, but were discouraged from starting any new activity during the trial. Physical therapy and local applications of pain relieving ointments/gels were not permitted. Patients were not prescribed any instructions or advice regarding diet or other life style change as per standard Ayurveda practice [10].

Laboratory investigations

Routine laboratory workup (haemogram and metabolic parameters including lipids, renal and hepatic function and urine analysis) was carried out at as per protocol. X-rays of knees were taken to confirm diagnosis. Commercially available ELISA kits were used to assay serum hyaluronic acid (Corgenix Inc. Broomfield, CO, USA) and urinary human type II collagen C-telopeptide (CTX-II) (Cartilaps, Nodic Biosciences, Denmark).

Adverse event

Patients were questioned at every visit for common drug-related symptoms as per a predetermined checklist and encouraged to add any other symptom they considered as a drug-related side effect.

Withdrawals

Patients could withdraw voluntarily or at the discretion of the investigator.

Statistical analysis

Equivalence ranges (Table 1) for each of the three primary efficacy variables were selected *a priori*. The range (95% CI) of minimal clinically significant change in pain VAS was chosen from an equivalence study of topical diclofenac solution and oral diclofenac [21]. A similar

TABLE 1 Difference between mean change from baseline to completion in primary efficacy variables by treatment groups: per protocol completer analysis

Interventions for comparison	95% CI (two-sided) of the difference for the parameter		
	Pain VAS (equivalence range ± 1.5 cm)	WOMAC pain (equivalence range ± 2.5)	WOMAC difficulty (equivalence range ± 8.5)
SGCG–glucosamine	−0.34 to 1.12	−0.75 to 1.31	−3.16 to 3.52
SGCG–SGC	−1.00 to 0.60	−1.70 to 0.46	−5.63 to 0.95
SGCG–celecoxib	−1.02 to 0.36	−1.48 to 0.52	−4.29 to 2.47
Glucosamine–SGC	−1.34 to 0.16	−1.93 to 0.13	−5.66 to 0.62
Glucosamine–celecoxib	−1.37 to −0.07	−1.72 to 0.20	−4.31 to 2.13
SGC–celecoxib	−0.85 to 0.59	−0.86 to 1.14	−1.74 to 4.60

An equivalence trial of Ayurvedic medicines (SGCG and SGC), glucosamine sulphate and celecoxib in knee OA. Pain VAS: active pain on weight-bearing activity on visual analogue scale (0–10 cm); WOMAC: questionnaire for functional evaluation of knee and hip; WOMAC pain: mild to severe categorical outcome (score 0–20); WOMAC difficulty: mild to severe categorical outcome (score 0–68). Equivalence ranges were determined *a priori* (see text for details).

range for WOMAC pain and WOMAC difficulty were adopted as recommended by Bellamy [17]. The trial was to be declared successful if equivalence was demonstrated for each of the primary efficacy variables.

The formula published by Jones *et al.* [22] was used to calculate the sample size of each intervention arm. Calculations were performed separately for each of the three primary efficacy variables (with usual standard type I error $\alpha = 0.05$ and power = 80%) and the maximum sample size (out of the three variables) obtained was multiplied by four to calculate the sample size. The final sample size was adjusted for an expected 20% dropout rate.

Both intention-to-treat analysis with the last observation carried forward and per protocol analysis (completers) were carried out using analysis of variance (ANOVA). The trial was designed with 80% power and a two-sided $P < 0.05$ was considered significant in all statistical tests. Intervention groups were compared for efficacy after adjusting for baseline mean values [analysis of covariance (ANCOVA)] and *P* adjusted for multiple comparison (using Bonferroni's method). The 95% CIs were computed for mean change in efficacy variables between intervention groups. The statistical software program SPSS version 12.5 (SPSS, Chicago, IL, USA) was used.

Results

A total of 440 eligible patients were randomized and allotted to treatment (Fig. 1). The groups were well matched (Table 2). A total of 126 (28.6%) patients withdrew from the study (Fig. 1). There were no significant differences between the groups except for 12 patients (5 SGCG, 4 SGC and 3 glucosamine) who withdrew due to a study drug-related adverse event (AE) [pruritus, epigastric discomfort, nausea, oral ulcers and elevated serum glutamic pyruvic transaminase (SGPT)/alanine aminotransaminase (ALT)]. Seven patients in the Ayurvedic intervention groups (3 SGC and 4 SGCG) were withdrawn due to a >3-fold rise above the upper limit of normal (ULN) in SGPT, which was accompanied by a mild rise in other liver enzymes and normal serum bilirubin and albumen; three had concealed a past history of chronic compensated hepatitis (two seropositive for hepatitis B virus).

Adverse events

There were no significant differences between the groups except for raised SGPT (Table 3). Clinically the AEs were predominantly mild and required only symptomatic treatment. None required hospitalization or any special/invasive intervention.

Twenty-six patients (11 SGCG, 4 glucosamine, 9 SGC and 2 celecoxib) in the study cohort showed an asymptomatic elevation in SGPT that was often accompanied by a proportionately smaller increase (<3 ULN) in other liver serum enzymes [aspartate aminotransaminase/serum glutamic oxalacetic transaminase (SGOT) and alkaline phosphatase (ALP)] and all other normal liver functions including serum bilirubin and normal eosinophil count. None reported a concurrent febrile illness and/or symptoms that could be related to a hepatic, biliary or pancreatic disorder. We could not screen all patients for hepatitis viruses. Altogether, an SGPT increase of >3-fold (but <6 times) ULN was observed in 10 patients in the Ayurvedic interventional groups at the 4-week follow-up. In all patients (withdrawals and those continued) with >3-fold rise, SGPT returned to normal by 8–12 weeks of follow-up.

There was no difference between the intervention groups at baseline for any of the serum liver enzymes (data not shown). However, on completion, the difference for SGPT (mean, mean change and ratio) was significantly (ANOVA) different by intervention groups (supplementary Table 2, available at *Rheumatology* Online) and higher values were observed in the Ayurvedic intervention groups.

Table 2 Demographic features and selected outcome variables at baseline

Variable	Drug code				*P* value (comparison, by ANOVA)
	SGCG (*n* = 103)	SGC (*n* = 102)	Glucosamine (*n* = 108)	Celecoxib (*n* = 105)	
Age (years)	55.55 (7.54)	55.28 (7.99)	55.51 (8.57)	56.6 (8.87)	0.24
Weight (kg)	67.38 (12.47)	65.55 (10.26)	66.43 (11.97)	64.43 (10.85)	0.28
Height (cm)	155.48 (7.89)	154.43 (8.99)	155.64 (10.02)	153.39 (8.34)	0.23
BMI	28.03 (5.58)	27.71 (4.97)	27.46 (4.51)	27.44 (4.61)	0.81
Disease duration[a] (months)	55.24 (47.88)	53.93 (54.99)	58.65 (56.94)	51.54 (46.68)	0.80
Active pain VAS (0–10 cm)	6.56 (1.24)	6.39 (1.59)	6.53 (1.20)	6.55 (1.25)	0.76
WOMAC pain (0–20)	9.33 (3.31)	9.44 (2.89)	9.33 (3.37)	9.43 (2.83)	0.99
WOMAC difficulty (0–68)	32.62 (11.11)	33.33 (10.77)	32.03 (11.04)	34.3 (10)	0.45
Patient global assessment (1–5)	3.6 (0.65)	3.59 (0.65)	3.58 (0.67)	3.59 (0.63)	0.99
Physician global assessment (1–5)	3.17 (0.49)	3.15 (0.43)	3.18 (0.49)	3.23 (0.49)	0.64
HAQ (0–24)	7.35 (2.58)	7.63 (2.60)	6.78 (2.51)	7.33 (2.72)	0.11

An equivalence trial of Ayurvedic medicines (SGCG and SGC), glucosamine sulphate and celecoxib in knee OA. Values are given as mean (S.D.). WOMAC: questionnaire for hip and knee function (see text for details). [a]Symptomatic knee OA.

Table 3 Incidence of adverse events

Adverse events	SGCG (*n* = 103)	SGC (*n* = 102)	Glucosamine (*n* = 108)	Celecoxib (*n* = 105)
Epigastric discomfort	10 (9.71)	15 (14.71)	16 (14.81)	18 (17.14)
Anorexia	1 (0.97)	0 (0)	4 (3.70)	1 (0.95)
Nausea	6 (5.83)	5 (4.90)	3 (2.78)	3 (2.86)
Vomiting	4 (3.88)	0 (0)	2 (1.85)	0 (0)
Diarrhoea	0 (0)	0 (0)	3 (2.78)	4 (3.81)
Constipation	6 (5.83)	2 (1.96)	4 (3.70)	8 (7.62)
Mucous ulcer	2 (1.94)	1 (0.98)	2 (1.85)	4 (3.81)
Skin rash and/or itching	3 (2.91)	4 (3.92)	3 (2.78)	5 (4.76)
Elevated SGPT	11 (10.68)	9 (8.82)	4 (3.70)	2 (1.90)
Total	29 (28.16)	33 (32.35)	34 (31.48)	34 (32.38)

An equivalence trial of Ayurvedic medicines (SGCG and SGC), glucosamine sulphate and celecoxib in knee OA. Data are number (%) of patients experiencing at least one episode of the event.

Efficacy

Significant improvement was seen in each of the intervention groups (Table 4). The differences between any two intervention groups for the mean change from baseline to completion for primary efficacy measure was within the equivalence range, both for intent-to-treat analysis (Table 5) and completers (Table 1). Pairwise comparison (ANCOVA with adjustment for baseline parameter values) of primary efficacy variables did not show consistent significant differences (supplementary Table 3, available at *Rheumatology* Online). Oral paracetamol consumption in the completers was negligible and did not differ by study groups (data not shown).

A significant reduction in urinary CTX-II was only observed in the SGCG interventional group (95% CI 1.04, 2.54). The study groups did not differ for serum hyaluronic acid or CTX-II (supplementary Table 4, available at *Rheumatology* Online).

Discussion

In this first-ever head-to-head comparison, Ayurvedic drugs (SGCG and SGC) were found equivalent to oral glucosamine sulphate and celecoxib in reducing knee pain and improving knee function in patients with knee OA over 24 weeks of treatment. The AEs in each of the intervention study groups were mild and comparable (Table 3) except for an unexpected increased incidence of asymptomatic high SGPT/ALT in patients treated with Ayurvedic drugs.

The current drug trial was a culmination of several experimental studies [8]. Current recommendations [23] require an equivalence clinical drug trial be preceded by

Table 4 Mean change (absolute and percentage) in efficacy from baseline to completion (24 weeks): intent-to-treat analysis

	SGCG	SGC	Glucosamine	Celecoxib	*P* (comparison, ANOVA)
Active pain VAS (0–10 cm)					
Mean change	−2.04 (−2.47, −1.61)	−2.06 (−2.54, −1.59)	−2.45 (−2.88, −2.03)	−1.82 (−2.20, −1.44)	0.21
Percentage change	31.10 (24.54, 37.65)	32.24 (24.88, 39.75)	37.52 (31.09, 44.10)	27.70 (21.98, 33.59)	
WOMAC pain (0–20)					
Mean change	−2.26 (−2.90, −1.62)	−1.79 (−2.44, −1.13)	−2.72 (−3.34, −2.10)	−1.90 (−2.48, −1.31)	0.14
Percentage change	24.22 (17.36, 31.08)	18.96 (11.97, 25.85)	29.15 (22.51, 35.80)	20.15 (13.89, 26.30)	
WOMAC difficulty (0–68)					
Mean change	−6.74 (−8.82, −4.66)	−5.85 (−7.65, −4.06)	−8.12 (−10.20, −6.04)	−6.93 (−8.85, −5.02)	0.45
Percentage change	20.66 (14.29, 27.04)	17.66 (12.18, 22.95)	25.37 (18.86, 31.85)	20.20 (14.64, 25.80)	
Patient global assessment (1–5)					
Mean change	−0.56 (−0.71, −0.41)	−0.61 (−0.76, −0.46)	−0.78 (−0.93, −0.62)	−0.53 (−0.67, −0.40)	0.09
Percentage change	15.56 (11.39, 19.72)	16.99 (12.81, 21.17)	21.79 (17.32, 25.98)	14.76 (11.14, 18.66)	
Physician global assessment (1–5)					
Mean change	−0.41 (−0.53, −0.30)	−0.60 (−0.72, −0.48)	−0.60 (−0.71, −0.49)	−0.46 (−0.57, −0.34)	0.04
Percentage change	12.93 (9.46, 16.72)	19.05 (15.24, 22.86)	18.87 (15.41, 22.33)	14.24 (10.53, 17.65)	
HAQ (0–24)					
Mean change	−1.43 (−1.97, −0.90)	−1.25 (−1.71, −0.80)	−1.24 (−1.65, −0.83)	−0.90 (−1.34, −0.45)	0.43
Percentage change	19.46 (12.24, 26.80)	16.38 (10.48, 22.41)	18.29 (12.24, 24.34)	12.28 (6.14, 18.28)	

An equivalence trial of Ayurvedic medicines (SGCG and SGC), glucosamine and celecoxib in osteoarthritic knees (95% CI shown in parenthesis). Pain VAS: active pain on weight-bearing activity on VAS (0–10 cm); WOMAC: range of score indicated with the variable (except pain, all other variables were categorical outcome) (see text for details).

TABLE 5 Difference between mean changes from baseline to completion in primary efficacy variables by treatment groups: intent-to-treat analysis

Interventions for comparison	95% CI (two-sided) of the difference for the parameter		
	Pain VAS (equivalence range ± 1.5 cm)	WOMAC pain (equivalence range ± 2.5)	WOMAC difficulty (equivalence range ± 8.5)
SGCG–glucosamine	−0.20 to 1.00	−0.50 to 1.32	−1.84 to 4.26
SGCG–SGC	−0.62 to 0.66	−1.42 to 0.42	−3.95 to 1.65
SGCG–celecoxib	−0.80 to 0.34	−1.11 to 0.61	−2.42 to 3.36
Glucosamine–SGC	−1.01 to 0.25	−1.70 to −0.12	−5.18 to 0.46
Glucosamine–celecoxib	−1.20 to −0.06	−1.52 to 0.20	−3.65 to 2.17
SGC–celecoxib	−0.85 to 0.35	−0.62 to 1.12	−1.03 to 4.27

An equivalence trial of Ayurvedic medicines (SGCG and SGC), glucosamine sulphate and celecoxib in knee OA. Pain VAS: active pain on weight-bearing activity on VAS (0–10 cm); WOMAC pain: mild to severe categorical outcome (score 0–20); WOMAC difficulty: mild to severe categorical outcome (score 0–68). Equivalence ranges were determined *a priori* (see text for details).

an unequivocal demonstration of superior efficacy to a placebo. We did not circumvent the need for a placebo control study [8]. The NMITLI strategy [8] required an interdisciplinary approach and was a novel and indigenous mix of science, economics and timelines.

In the first study step [8], 245 eligible patients with knee OA were treated with either of the five standardized Ayurvedic herbal formulations (common core ingredients), glucosamine sulphate or placebo over 16 weeks to demonstrate an overall best efficacy for an Ayurvedic C formulation [maximum reduction in active knee pain VAS (not significant), change in knee status (RIDIT analysis, $P < 0.05$) and least analgesic use ($P < 0.05$)]. The mean percentage improvement in active pain on completion was 18% in the placebo and 26% in the C formulation (not significant). In the next step, we selected C and B formulations [8] and ran a four-arm, randomized, single-blind dose escalation study [11] of 6-weeks' duration without permitting rescue analgesic and confirmed the safety of higher doses. The augmented C formulation retained superior efficacy and further showed an impressive reduction in the urinary C-telopeptide fragment of collagen II and was relabeled as SGC for use in the current trial. Also, a second formulation called SGCG (containing SGC ingredients and plant extract/*B. serrata*) was chosen.

Intriguingly, in parallel with the current trial, an *in vitro* experiment using an *ex vivo* cartilage explant model (chondrocyte cell culture) [13] demonstrated significant inhibition of the release of glycosaminoglycan and aggrecan (plus a transient reduction in nitric oxide release) by SGCG that was superior to SGC and comparable to glucosamine. This seems consistent with the reduction in urinary cartilage breakdown product (C-telopeptide) by SGCG in the current trial (supplementary Table 4, available at *Rheumatology* Online) and suggests a possible chondroprotective role [24].

For the current study, a trial of equivalence was selected rather than a placebo-controlled superiority trial. We were aware that an appropriate active control drug trial does provide assurance of assay sensitivity when combined with historical evidence of sensitivity to drug effects, as is the case with Ayurveda. The current trial was an unprecedented four-arm multicenter trial with sufficient power, suitable sample size and a conservative *a priori* equivalence range. The current study showed equivalence for each of the primary efficacy variables. In retrospect, we realized that our equivalence ranges were rather wide, especially in the case of WOMAC pain and difficulty. Our primary results (Tables 1 and 5) could have satisfied a narrower range of equivalence margin and further strengthened our conclusion. Also, the paired group analysis (supplementary Table 3, available at *Rheumatology* Online) did not show any consistently significant differences between any of the Ayurvedic interventions and the active comparators.

Based on clinical experience, we used a higher daily divided dose (2 g daily) of oral glucosamine sulphate instead of the traditional 1500 mg daily dose [4, 25] and the clinical efficacy (Table 4) was indeed impressive. Due to safety issues, we were compelled to used celecoxib 200 mg daily in three equally divided doses, which may be responsible for the lower efficacy and good safety (Table 3).

We included a placebo arm in the 16-week duration exploratory controlled evaluation of the short-listed Ayurvedic formulation that was completed prior to the current study [9]. Though not statistically significant in the reduction of pain, the candidate formulation for the current trial showed statistically significant improvement for several other efficacy variables [9]. So, in the planning of the current drug trial, we were advised (ethics committee) against a placebo arm. Placebo response in OA drug trials is reportedly high [5, 26]. The current Ayurvedic medications were not controlled for placebo response. However, the active comparators in the current drug trial (glucosamine and celecoxib) were shown to be superior to placebo by several controlled studies [26] and are the standard of care in several countries. In the recent

GUIDE trial [27], the mean percentage change/improvement on completion (24 weeks) for WOMAC pain in the placebo intervention was reportedly in the range 20–23% (intent-to-treat analysis); the corresponding improvement with glucosamine was 33–35%. In an earlier placebo-controlled study [20] of 32 weeks duration in knee OA, we demonstrated a significantly superior efficacy with the Ayurvedic drug. The mean percentage improvement in active pain (VAS and WOMAC) in the current study (Table 4) for each of the study interventions was much higher than the historical data for placebo described above.

The holistic therapeutic approach and safe use of Ayurvedic medicines is borne out by several centuries of clinical use [7] and is extremely endearing to our community. The safety profile (Table 3) for all study intervention groups was impressive. Six per cent of patients in the current study showed an asymptomatic, more or less solitary rise in SGPT. However, in seven patients with no prior liver disease and receiving Ayurvedic drugs, the increase was significant (3- to 5-fold ULN). None of the patients satisfied Hy's law of significant drug-induced liver injury (DILI) as described by the US Food and Drug Administration [28]. To the best of our knowledge, the current Ayurvedic formulations are not known to cause DILI. Prompted by the dosing study [11], we used higher doses as compared with routine clinical practice and standard texts [9, 10], and this might have contributed to DILI in susceptible cases. It is difficult to speculate on the precise cause of increased SGPT [29], and further investigation is required [28]. Several drugs in routine clinical use raise serum liver enzymes and this phenomenon is also used to monitor the optimum therapeutic effect of methotrexate. Interestingly, about 20% of patients treated with acetaminophen in the GUIDE study trial (glucosamine) showed abnormal liver function tests [27].

Several difficult-to-treat disorders in the modern context may be amenable to Ayurveda treatment. We have published contemporary reviews [7, 30] and carried out several drug trials [15, 20, 31, 32]. India is a rich source of ethnically recognized medicinal plants that have yet to be scientifically validated for therapeutic use [33]. In retrospect, the current trial satisfied several of the recent requirements for validation of botanical drugs [34] and is in concert with the CONSORT guidelines [35]. It is prudent to add that the current drug trial was planned long before the NIH-sponsored landmark trial demonstrated lack of efficacy of glucosamine hydrochloride [36]. We chose glucosamine sulphate because several drug trials support its efficacy [4, 27].

Our study has several other limitations. A high proportion of patients withdrew from the study (29%) (Fig. 1). We carried out a large patient population screen (Fig. 1) in government-run medical institutions and enrolled consenting patients who lived in fringe urban areas or nearby villages and encountered cumbersome logistics. Unfortunately there was also an unexpected epidemic of chikungunya and/or dengue in 2006 [37] and several patients fell prey to acute severe musculoskeletal pains. Another important caveat was that we did not use the traditional Ayurvedic holistic approach to treat patients. We intend to carry out whole system approach/pragmatic trials in the future [38].

There are several other unique aspects. The constituents of the current Ayurvedic study formulations are supposedly used to promote health and enhance the immune system in a non-specific manner [9, 10]; such properties are called rasayana [7, 9, 30] in Ayurveda. We used an Indian version of the validated Stanford HAQ and found impressive improvement (Table 4) with the Ayurvedic drugs and glucosamine. We completed the current NMITLI arthritis project to validate Ayurvedic drugs in 6 years [8]. As a result, we developed an Ayurvedic drug development and validation model that was socioeconomically attractive [8].

We have demonstrated an unequivocal clinical therapeutic equivalence between two standardized Ayurvedic formulations (SGCG and SGC) and glucosamine and celecoxib in the symptomatic treatment of osteoarthritic knees. The Ayurvedic drug SGCG is promising for future clinical use. A longer study period would be required to endorse its long-term efficacy and safety, especially with reference to hepatic effects. Ethnic medicines and medicinal plants must be explored to fulfill some of the unmet need for chondroprotective agents in the long-term management of OA. Studies such as ours also strengthen the contemporary mantra of comparative effectiveness.

Rheumatology key messages

- OA is predominantly treated with potentially toxic analgesics.
- Ayurveda (India) medicines also treat arthritis.
- Ayurvedic drugs, glucosamine and celecoxib were proven equivalent in a controlled clinical study of osteoarthritic knees.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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