Q J Med 2006; **99**:841–850
doi:10.1093/qjmed/hcl118

Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: a randomized placebo-controlled pilot study

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Received 11 May 2006 and in revised form 15 August 2006

Summary

Background: Osteoarthritis (OA) of the knee is the most prevalent joint disorder. Previous studies suggest that bromelain, a pineapple extract, may be a safer alternative/adjunctive treatment for knee OA than current conventional treatment.
Aim: To assess the efficacy of bromelain in treating OA of the knee.
Design: Randomized, double-blind placebo-controlled trial.
Methods: Subjects ($n=47$) with a confirmed diagnosis of moderate to severe knee OA were randomized to 12 weeks of bromelain 800 mg/day or placebo, with a 4-week follow-up. Knee (pain, stiffness and function) and quality-of-life symptoms were reported monthly in the WOMAC and SF36 questionnaires, respectively. Adverse events were also recorded. The primary outcome measure was the change in total WOMAC score from baseline to the end of treatment at week 12. Longitudinal models were used to evaluate outcome.
Results: Thirty-one patients completed the trial (14 bromelain, 17 placebo). No statistically significant differences were observed between groups for the primary outcome (coefficient 11.16, $p=0.27$, 95%CI −8.86 to 31.18), nor the WOMAC subscales or SF36. Both treatment groups showed clinically relevant improvement in the WOMAC disability subscale only. Adverse events were generally mild in nature.
Discussion: This study suggests that bromelain is not efficacious as an adjunctive treatment of moderate to severe OA, but its limitations support the need for a follow-up study.

Introduction

Osteoarthritis (OA) of the knee joint is the most prevalent joint disorder. For example, 6% of US adults aged >30 years[1] and 10% of the UK population aged >55 years[2] have the condition. It is associated with a high risk of disability.[3] Conventional treatment is aimed at symptomatic relief, i.e. decreasing pain and improving function. First-line treatment is paracetamol, but non-steroidal anti-inflammatory drugs (NSAIDs) are also frequently used. The high incidence of gastrointestinal adverse events (AE) associated with NSAIDs is well documented,[4,5] and an effective alternative treatment option would thus be of interest.

Bromelain, a crude, aqueous extract obtained from the pineapple plant, contains a number of proteolytic enzymes[6,7] that are considered to have a range of beneficial properties (reviewed

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in references 6–8), such as anti-inflammatory and analgesic actions, and anti-oedematous, antithrombotic and fibrinolytic effects.[7] Its anti-inflammatory effects are thought to be mediated by: (i) increasing serum fibrinolytic activity,[9] thus reducing plasma fibrinogen levels[10] and decreasing bradykinin levels (which results in reduced vascular permeability), and hence reducing oedema and relieving pain;[11] and (ii) mediating prostaglandin levels (by decreasing levels of PGE_2 and thromboxane A_2). Analgesic properties have been demonstrated in a variety of models,[12–14] and are thought to be a result of a direct influence on pain mediators (e.g. bradykinin[11]), as well as indirect effects through anti-inflammatory actions (e.g. reduction in oedema, debris and immune complexes).

A number of clinical trials[15–19] have assessed the use of bromelain in joint inflammation, and these have been reviewed.[20] They have been either open studies[15,19] or equivalence studies designed to assess the comparative effectiveness against standard NSAID treatment.[16–18] Their findings suggest that bromelain may be beneficial in the treatment of OA, and as effective as standard NSAID treatment. In addition, safety reports reveal no serious adverse reactions, and tolerability appears good. Although minor adverse events have been reported, these are mainly confined to mild gastrointestinal symptoms. However, there are a number of methodological concerns surrounding these studies. Firstly, the period of treatment in these arthritic studies is much shorter (average 3–4 weeks) than that used in clinical practice (3–4 months). Hence, the safety and efficacy of longer-term treatment is unknown. In addition, comparison of efficacy between trials is problematic, since the dosage varies. Finally, in all but one (open) study, bromelain was used in conjunction with other additional proteolytic enzymes of variable doses; leaving doubts about the specific efficacy of bromelain alone.

This study was a double-blind placebo-controlled pilot trial, using a single standard dose of bromelain for 12 weeks in patients with moderate-to-severe osteoarthritis of the knee. Its aims were to assess bromelain's specific efficacy and safety profile, and to develop more rigorous methodology for a definitive study, based on the effect size identified in this pilot. The dose selected was based on the results of previous studies and current clinical practice. The null hypothesis was that bromelain has no anti-inflammatory properties (as assessed by the reduction in pain, stiffness and disability aspects on the WOMAC) in chronic osteoarthritis of the knee after 3 months of treatment, as compared to placebo.

Methods

Design

This was a double-blind randomized parallel-group placebo-controlled trial. Subjects were recruited from advertisements in the local press, and were screened over the telephone to ensure they had suffered constant knee pain in the previous 30 days. Inclusion criteria were age >40 years, diagnosis of OA in at least one knee joint (ACR classification for knee OA[21]) confirmed by X-ray, knee pain on most days of the last month, morning stiffness of <30 min, stiffness with resting the joint and stable use of medication (conventional/complementary, including nutritional medicine) for >3 months. Exclusion criteria were those who had very severe or doubtful OA diagnosis (i.e. those with a Grade 1 Kellegren and Lawrence score from the knee X-ray), those unwilling or unable to comply with study procedures, including those with severe co-morbidities, other known rheumatic conditions, current or recent (>1 month) corticosteroid treatment, contraindications to medication (i.e. those taking oral anticoagulants, e.g. warfarin[22]), or renal disease, those pregnant or trying to become pregnant or breastfeeding.

Medication, randomization and blinding

Subjects were allocated to bromelain (two tablets of one-a-day Bromelin (Lichtwer Pharma UK) twice per day, i.e. 800 mg/day) or placebo (two tablets containing placebo twice per day). The bromelain used for the tablets was obtained from pineapple stems, and contained a mixture of standardized enzymes (FIP units). The enzyme mixture was not purified further. An independent company was responsible for coding, packaging and labelling the study medication, and the pharmacy at the study centre dispensed the pre-coded study medication to the subjects by post in accordance with the randomization allocation.

Patients were randomized to treatment allocation by a computer-generated minimization method,[23] with stratification for both gender and severity of osteoarthritis (i.e. grade 2, 3 or 4). The randomization coding, secured in a sealed envelope, was held by two researchers not involved with data collection or analysis (RM and GL) until data entry was complete, and was only opened during the trial in the case of serious adverse events. The code was broken by the statistician only after data entry was completed, the primary outcome determined and any data queries resolved. Subjects and trial investigators were blinded to treatment allocation. The security of the blinding process was assessed

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by asking both subjects and investigator to guess which treatment they believed the subject received at the end of the subject's trial period.

Procedures

The study procedure is shown in Figure 1. Ethical approval was granted from the Southampton and South West Hampshire Local Ethics committee for the study (ethics number 340/02/t). Interested participants were posted the patient information sheet, and attended a screening clinic visit at a private medical clinic, where written informed consent was obtained. Subjects were screened to confirm a diagnosis of OA in a single specified knee joint. In addition, information on medical history, medication use, average knee pain over the previous month (as identified by a minimum of 30 mm on the pain subscale of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index[24]) were collected. All subjects underwent X-ray at a local private hospital (BUPA, Southampton), and blood samples were taken to exclude diagnoses other than OA.

Subjects were randomized to treatment following confirmation of the diagnosis of OA. Outcomes measures were recorded by the subjects at weekly and monthly intervals. Each volunteer received a weekly telephone call to monitor compliance and adverse events, and were advised to seek advice and treatment from their general practitioner in the event of any exacerbation. Subjects attended for a final clinic visit at the end of the follow-up period, when they reported their overall perceived level of pain relief due to the study medication (on a scale of 1 to 7, where 1 = very poor relief and 7 = very good relief).

Measures

The primary outcome measure, the Western Ontario and McMaster Universities Osteoarthritis Index[24] (WOMAC), is a disease-specific validated measure which measures pain, stiffness and function and was recorded at monthly intervals. The WOMAC gives scores for each single construct in addition to a global score. Two summary scores (physical function and mental functioning) from the validated quality-of-life measure SF36[25] were also reported on a monthly basis during the trial. In addition, the patient's Global Assessment (a validated scale to assess weekly global well-being[26]), changes in osteoarthritis medication and missed study medication were recorded on a weekly basis. Subjects completed the adverse event monitoring form as necessary. Event descriptions, their severity (mild, moderate or severe), duration and their perceived relationship to the study medication (probable, possible, unlikely, not related and not sure) were self-reported.

Outcomes

The primary outcome measure was the change in mean global WOMAC score from baseline to week 12. Secondary outcomes were: (i) changes in WOMAC subscales (i.e. pain, stiffness and function) scores from baseline to week 12; (ii) changes in quality of life assessment from baseline to week 12; (iii) changes in weekly global assessment from baseline to week 12; (iv) the level and type of adverse event reporting; and (v) perceived overall pain relief. The security of the blinding process was assessed from the 'guess the treatment' responses.

Statistical analyses

Sample size was not calculated before the trial, as no previous study had assessed bromelain as a single constituent using WOMAC as the primary outcome measure. This study was therefore run as an exploratory trial, not powered to be definitive, but to provide the basis for sample size calculation for a possible future definitive study. We proposed that a sample of 60 subjects (30 per arm) with an estimated drop-out rate of 15–20% (i.e. 50 patients completing the trial) was sufficient for our aims. A sample of $n = 25$ per arm, based on 80% power and 5% significance level, would enable us to detect a 7.5 mm difference in respect of the primary outcome (WOMAC total score). The smallest clinical significance improvement in WOMAC is considered to be a change of 9–12 mm in one of the WOMAC subscales;[27–29] thus a reduction of between 27–36 mm would be expected for the WOMAC global score (the sum of the changes for each of the three subscales). If bromelain has equivalent efficacy to standard conventional treatment (NSAIDs), a sample size calculation based on a study assessing a standard treatment (e.g. rofecoxib[30]), suggests that $n = 50$ patients per group would be needed to detect a difference of 12 mm on WOMAC subscales between treatment and placebo groups, based on 80% power and 5% significance level.

The randomization code was broken after data analysis. The data were analysed with statistical significance set at $p < 0.05$ to compare changes in scores from baseline to the end of treatment. Longitudinal analysis using first-order autoregressive correlation structure and generalized estimating equations (STATA version 5) was used to fit models to the treatment and post treatment scores for the primary and secondary outcome measures,

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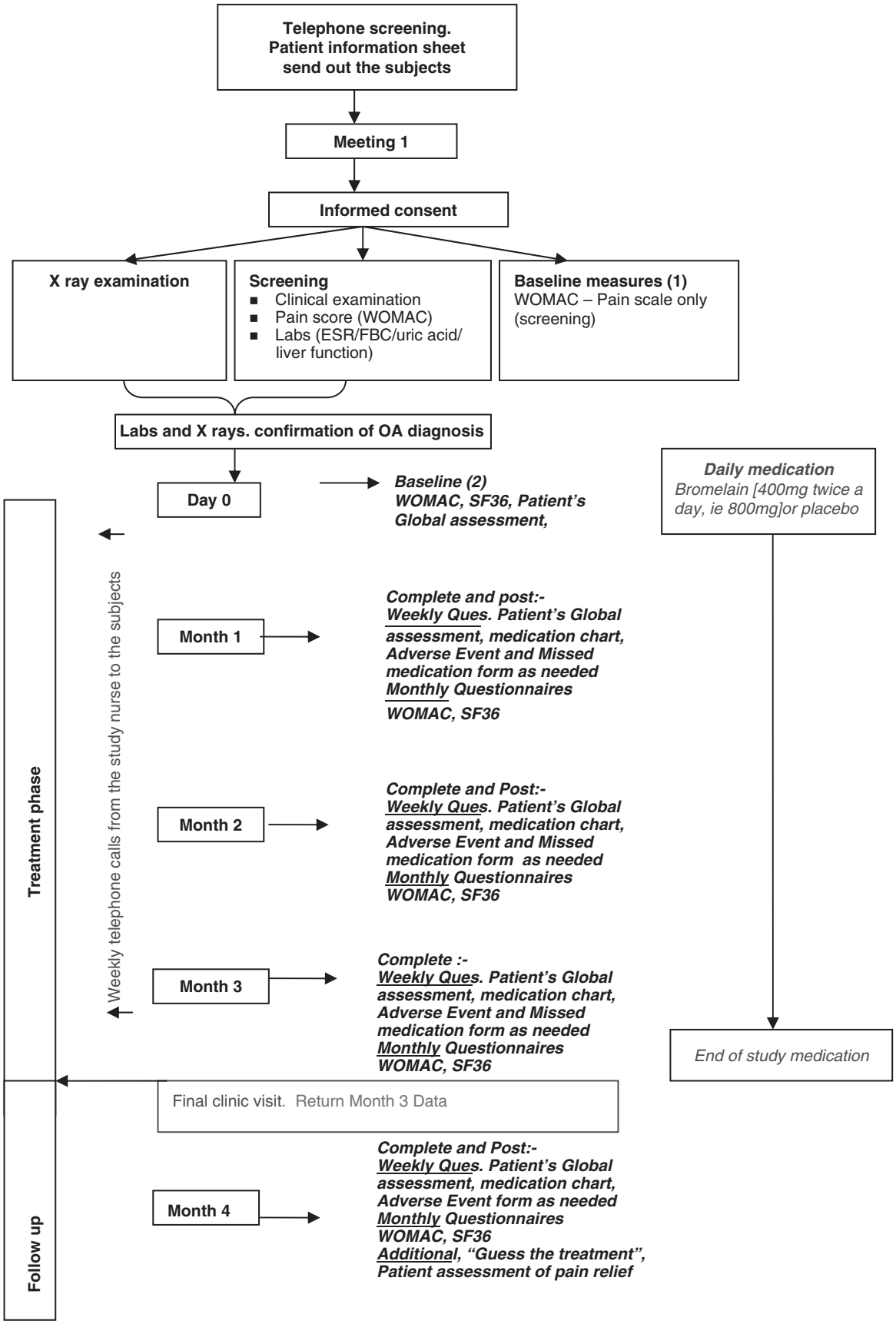

Figure 1. Flow chart of study procedure.

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including adjustments for baseline and other covariates. No missing values were imputed; this method fits all available data to the model. This analytical modeling method was appropriate, since only 31 of the initial 47 subjects had complete data; longitudinal analysis is more suitable for the analysis of time series data where there are missing data due to dropouts, since it minimizes bias introduced by using imputational methods such as last observation carried forward when using repeated measures ANOVA.[31] Adverse events were reported using descriptive statistics. Mean differences in perceived overall pain relief were identified by paired t tests. Assessment of blinding ('guess the treatment') was identified by χ^2 test.

Results

Sixty-one subjects were invited to the initial recruitment interview. Forty-seven met all the inclusion criteria and were randomized to treatment (Figure 2), and 31 completed the trial. Recruitment to randomization was underachieved, due to time constraints imposed on the trial by limited funding. The treatment groups were balanced at entry (Table 1) except for duration of osteoarthritis since diagnosis. Placebo-treated subjects were diagnosed with knee osteoarthritis for a mean of 2.9 years longer than those who received bromelain. Blinding of treatment allocation (as assessed by 'guess the treatment') was confirmed secure for both the study nurse ($\chi^2 = 0.784$, df = 1, $p = 0.376$) and the subjects ($\chi^2 = 0.140$, df = 1, $p = 0.709$).

Primary outcome

Mean total WOMAC scores for each treatment group for baseline and months 1–4 are shown in Table 2. A longitudinal model for these total scores was investigated to estimate the effects of time and treatment (and also a number of covariates such as age, gender, years since diagnosis, baseline WOMAC total score). No statistical significant difference in improvement was observed in mean group global scores from baseline to end of treatment at 12 weeks (treatment coefficient of 11.16, 95%CI −8.86 to 31.18). A reduction in mean global scores was identified for both groups, with that for the bromelain group being clinically relevant.

Secondary outcomes

WOMAC subscales

Mean scores per treatment group for each subscale are shown in Table 2. As for the total score, longitudinal models were fitted for each sub-scale, including the corresponding baseline subscale score as covariate. No statistical (nor clinically) significant treatment group difference in mean scores was observed for either the pain (coeff. 1.92, $p = 0.22$, 95%CI −2.87 to 6.71) nor the stiffness subscale (coeff. 0.013, $p = 0.992$, 95%CI −2.46 to 2.48). Both treatment groups demonstrated a clinically significant reduction in mean disability scores (21.8 mm bromelain group; 9.84 mm placebo group), but no statistically significant group difference was noted from baseline to week 12 (coeff. 8.92, $p = 0.210$, 95%CI −5.02 to 22.85).

Quality of life (SF36)

Mean scores per treatment group for both the overall physical and mental components are shown in Table 3. No significant group differences were identified for either the physical (coeff. −2.76, $p = 0.17$, 95%CI −6.69 to 1.16) or the mental component (coeff. 0.73, $p = 0.65$, 95%CI −2.43 to 3.89).

Weekly global assessment

There was no significant change in weekly global assessment from baseline to week 16 (mean score difference for bromelain 0.28, a 5.7% reduction, vs. placebo 0.35, a 7.2% reduction; coeff. 0.13, $p = 0.608$, 95%CI −0.35 to 0.60).

The level and type of adverse event reporting

Fifty-six adverse events were reported in total (28 in each group) by a total of 28 subjects (bromelain $n = 15$, 62.5% of bromelain group; placebo $n = 13$, 56.5% of placebo group). The majority of adverse events occurred during the first 4 weeks of treatment (57% bromelain; 50% placebo). Overall, 32 adverse events (bromelain group 18; placebo group 14) were classified by the subjects as being either 'probably' or 'possibly' related to the study medication, i.e. adverse drug reactions (ADR) (Table 4). Subjects classified nine of these events as severe (6 bromelain, 3 placebo). These probably or possibly related symptoms were (for the bromelain group): gastrointestinal problems ($n = 10$); headache ($n = 2$); bad dreams ($n = 1$); dry mouth ($n = 1$); and stiffness or painful knees ($n = 4$). The majority of GI problems reported (80%) occurred mainly in month one, and the symptoms reported were flatulence, diarrhoea, stomach distension and constipation, two of which were reported as being severe. In addition, two serious adverse events (SAE) were reported (both subjects receiving bromelain), both unrelated to the study medication: a hospitalization due to suspected

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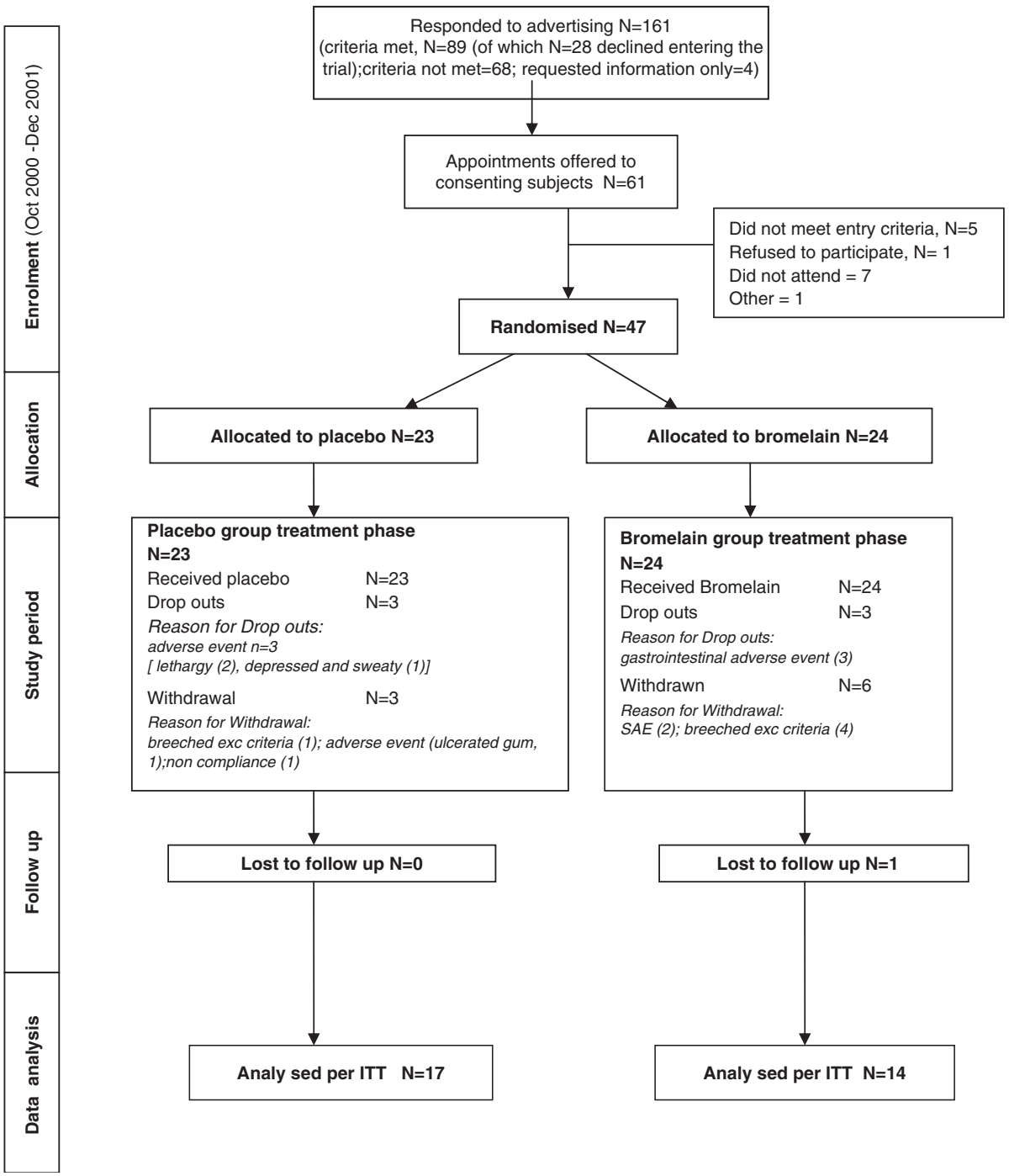

Figure 2. CONSORT diagram.

brain tumour; and another hospitalization due to bradycardia. The randomization coding was therefore opened twice during the study period for these two SAEs.

Perceived overall pain relief

There was no significant difference (mean score difference 0.46, $p = 0.465$, 95%CI −0.81 to 1.72) between treatment groups with respect to perceived pain relief.

Discussion

This pilot study investigated the efficacy of bromelain as a sole treatment for proven osteoarthritis of the knee using a double-blind, randomized,

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Table 1 Descriptive data for the two intervention groups at baseline

Baseline measure	Bromelain		Placebo		Mean difference, p
	Mean	SD	Mean	SD	
n	24		23		
Age (years)	62.83	9.36	60.43	7.63	2.40, $p=0.342$
Sex (F:M)	13:11		11:12		
BMI (kg/m^2)	29.14	6.21	31.08	7.21	1.94, $p=0.328$
Time since diagnosis (years)	4.79	3.61	7.70	5.51	2.90, $p=0.037$*
Baseline plasma CRP concentration (μmol)	6.41	8.34	6.87	12.05	0.46, $p=0.880$
Current use of CAM medication for knee OA (numbers)	10		7		
Current use of conventional medication for knee OA (numbers)	16		19		
X-ray assessment of OA severity (numbers)					
Kellgren and Lawrence score 2	7		7		
Kellgren and Lawrence score 3	9		9		
Kellgren and Lawrence score 4	8		7		
Mean score	1.58	0.50	1.43	0.51	0.15, $p=0.319$

OA, osteoarthritis; BI, body mass index; CAM, complementary/alternative medicine; CRP, C-reactive protein. *$p<0.05$.

Table 2 WOMAC scores (mm) over time

Treatment	Study period				Follow-up (Week 16)	Analysis
	Baseline	Week 4	Week 8	Week 12		
Total score						
Bromelain	117.59 ± 34.23 ($n=24$)	94.22 ± 46.73 ($n=22$)	89.20 ± 43.60 ($n=17$)	85.70 ± 45.17 ($n=15$)	96.03 ± 47.71 ($n=14$)	Coeff. = 11.16 $p=0.27$
Placebo	112.84 ± 49.28 ($n=23$)	101.00 ± 55.33 ($n=18$)	92.44 ± 50.49 ($n=17$)	93.07 ± 53.10 ($n=17$)	91.89 ± 55.75 ($n=17$)	95%CI −8.86 to 31.18
Pain subscale						
Bromelain	23.01 ± 9.18 ($n=24$)	19.21 ± 9.66 ($n=22$)	17.43 ± 8.34 ($n=17$)	15.61 ± 10.27 ($n=15$)	18.58 ± 10.47 ($n=14$)	Coeff. = 1.92 $p=0.22$
Placebo	25.67 ± 11.43 ($n=23$)	20.07 ± 12.77 ($n=18$)	18.22 ± 11.18 ($n=17$)	18.81 ± 10.84 ($n=17$)	17.98 ± 12.65 ($n=17$)	95% CI −2.87 to 6.71
Stiffness subscale						
Bromelain	10.28 ± 5.64 ($n=24$)	8.78 ± 4.42 ($n=22$)	7.92 ± 4.97 ($n=17$)	7.94 ± 5.59 ($n=15$)	8.92 ± 4.20 ($n=14$)	Coeff. = 0.01 $p=0.9995\%$
Placebo	12.07 ± 4.84 ($n=23$)	10.15 ± 5.54 ($n=18$)	7.74 ± 4.05 ($n=17$)	9.00 ± 4.96 ($n=17$)	8.40 ± 5.31 ($n=17$)	CI −2.46 to 2.48
Disability subscale						
Bromelain	84.31 ± 25.12 ($n=24$)	66.24 ± 35.62 ($n=22$)	63.14 ± 32.22 ($n=17$)	62.50 ± 31.12 ($n=15$)	68.53 ± 34.16 ($n=14$)	Coeff. = 8.92 $p=0.21$
Placebo	75.11 ± 37.68 ($n=23$)	67.38 ± 38.56 ($n=18$)	66.48 ± 36.58 ($n=17$)	65.27 ± 38.07 ($n=17$)	65.51 ± 39.05 ($n=17$)	95%CI −5.02 to 22.85

Data are means ± SD. Coeff., estimated effect of bromelain versus placebo in the longitudinal analysis. Minimal clinically relevant improvement for each subscale is 9 mm reduction from baseline to end of treatment at week 12; for global score, 27 mm. A decrease in all scores indicates an improvement in symptoms relating to that scale.

placebo-controlled trial. Previous studies assessing bromelain suggested that bromelain may have benefits in the treatment of joint inflammation and may have equivalence to standard conventional medication for this condition. Our results suggest this is not the case. The absence of statistical difference between treatment groups in this trial suggests that any difference in patient-relevant outcomes is small, and apart from the disability subscale (and therefore the global score), not clinically relevant. Based on this effect size, a definitive study to detect a group difference of

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Table 3 Mean scores for physical and mental components of the SF36

Treatment	Study period					Longitudinal analysis
	Baseline	Week 4	Week 8	Week 12	Week 16	
Physical component						
Bromelain	33.42	36.23	37.37	37.57	37.74	Coeff. = −2.76
	(n = 24)	(n = 21)	(n = 18)	(n = 15)	(n = 14)	p = 0.17
Placebo	33.34	34.84	35.14	34.63	32.97	95%CI −6.69 to 1.16
	(n = 23)	(n = 18)	(n = 17)	(n = 17)	(n = 17)	1.16
Mental component						
Bromelain	47.76	46.63	45.55	46.09	44.37	Coeff. = 0.73
	(n = 24)	(n = 21)	(n = 18)	(n = 15)	(n = 14)	p = 0.65
Placebo	45.63	46.21	46.05	45.68	46.66	95%CI −2.43 to 3.89
	(n = 23)	(n = 18)	(n = 17)	(n = 17)	(n = 17)	

Data are means. Coeff., estimated effect of bromelain vs. placebo in the longitudinal analysis. An increase in scores indicates an improvement in symptoms.

Table 4 Possible or probable Adverse Drug Reactions (ADRs) reported during the study period

	Week 4	Week 8	Week 12	Week 16 (follow-up)	Total study period
Bromelain group					
ADRs	14	0	2	2	18
Severity	Mild 8	Mild 0	Mild 0	Mild 0	Mild 8
	Moderate 1	Moderate 0	Moderate 2	Moderate 1	Moderate 4
	Severe 5	Severe 0	Severe 0	Severe 1	Severe 6
Placebo group					
ADRs	9	3	0	1	14
Severity	Mild 7	Mild 1	Mild 0	Mild 1	Mild 9
	Moderate 1	Moderate 0	Moderate 0	Moderate 0	Moderate 1
	Severe 1	Severe 2	Severe 0	Severe 0	Severe 3

10 mm on the WOMAC subscale, which would be clinically relevant in this group of patients with 80% power, would require a sample size of 130 per group. This sample size is considerably larger than the numbers needed to show efficacy using standard conventional treatment such as NSAIDs (n = 50 per group), and suggests that bromelain does not have equivalent efficacy to conventional anti-inflammatory medications.

We believe that our data are robust. The baseline data showed that apart from duration of OA symptoms, the two treatment groups were balanced at entry, and we do not think that any selection bias at entry confounded outcome. There were nine drop-outs in the bromelain group and six in the placebo group at week 12, the relevant period for analysis. Two of the drop-outs in the bromelain group were for serious adverse events unrelated to the study. While this level of drop-outs is not ideal, we think it unlikely that it has seriously compromised our interpretation of the data. Clinically, patients with longer duration of disease may be harder to treat. As the placebo group patients had the longer duration of disease, any resulting bias towards a treatment benefit would have been in favour of the bromelain group. The blinding assessment confirmed that the process of blinding was secure. Covariates (age, sex, duration of OA symptoms) were also evaluated, and shown to have no significant effect on outcome. The drop-out rate of 12% (6/47) is acceptable for a study of this duration.

There are a number of issues to be considered when interpreting this data. The dosage used in this study was within the range previously identified as having therapeutic action (i.e. 160–2000 mg/day[7]), appeared to have a good safety profile and unlike previous trials, was given for a clinically appropriate duration. The medication appeared to be well tolerated, with low rates of drop-outs and adverse events; only 20% of the GI adverse events which were perceived as being related to the study

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medication were classified by the subject as being severe. However the optimal dose for treating patients with moderate-to-severe knee OA is as unknown, as no Phase II trial has been conducted. Previous (open or comparative) studies have used lower doses in OA knee, and have demonstrated favourable responses; however, despite using larger doses in this trial, no effects of efficacy over placebo were identified. Another consideration is that bromelain was used in this study in a conventional manner to treat a single indication, and this does not reflect how a herbalist might prescribe it. Nevertheless, evaluating the use of bromelain in this way may reflect its more pragmatic use, i.e. as an over the counter medication as an alternative or an adjunct to conventional therapy for OA. Finally, the issue of potential bias in favour of bromelain group, with respect to the years since diagnosis, would be expected to accentuate the levels of clinical improvement between treatment groups, and this was not seen.

In conclusion, the data from this study failed to identify efficacy for bromelain as an adjunctive treatment versus placebo.

Acknowledgements

This study was funded by Lichtwer Pharma UK and Boots plc. Medications were supplied free of charge by Lichtwer Pharma UK. Dr Brien's fellowship was funded by the Hospital Savings Association. Dr Lewith's post is funded by a grant from the Rufford Maurice Laing Foundation. Dr Walker's post was funded by the University of Reading, and Dr Bundy's fellowship was funded by Lichtwer Pharma UK. We thank Trish Boyle for data collection, and Janet O'Hara at Lloyds Chemist, Winchester, for randomization, Debby Layton for her advice on the analysis of adverse events during the protocol development stage, and Mrs Jackie Clarke, Pharmacy, The Centre for the Study of Complementary Medicine, Southampton, who dispensed and posted the study medication.

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