Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial

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Summary

Background We aimed to investigate whether the addition of non-steroidal anti-inflammatory drugs or spinal manipulative therapy, or both, would result in faster recovery for patients with acute low back pain receiving recommended first-line care.

Methods 240 patients with acute low back pain who had seen their general practitioner and had been given advice and paracetamol were randomly allocated to one of four groups in our community-based study: diclofenac 50 mg twice daily and placebo manipulative therapy (n=60); spinal manipulative therapy and placebo drug (n=60); diclofenac 50 mg twice daily and spinal manipulative therapy (n=60); or double placebo (n=60). The primary outcome was days to recovery from pain assessed by survival curves (log-rank test) in an intention-to-treat analysis. This trial was registered with the Australian Clinical Trials Registry, ACTRN012605000036617.

Findings Neither diclofenac nor spinal manipulative therapy appreciably reduced the number of days until recovery compared with placebo drug or placebo manipulative therapy (diclofenac hazard ratio 1·09, 95% CI 0·84–1·42, p=0·516; spinal manipulative therapy hazard ratio 1·01, 95% CI 0·77–1·31, p=0·955). 237 patients (99%) either recovered or were censored 12 weeks after randomisation. 22 patients had possible adverse reactions including gastrointestinal disturbances, dizziness, and heart palpitations. Half of these patients were in the active diclofenac group, the other half were taking placebo. One patient taking active diclofenac had a suspected hypersensitivity reaction and ceased treatment.

Interpretation Patients with acute low back pain receiving recommended first-line care do not recover more quickly with the addition of diclofenac or spinal manipulative therapy.

Introduction

Present treatment guidelines[1,2] for acute low back pain recommend that general practitioners should give advice (remain active, avoid bed rest, and reassurance of favourable prognosis) and paracetamol as the first line of care. Non-steroidal anti-inflammatory drugs (NSAIDs) and spinal manipulative therapy are recommended[1,2] as second-line management options for patients who have slow recovery. We do not know whether NSAIDs or spinal manipulative therapy, or both, in addition to advice and paracetamol as initial treatment results in quicker recovery for such patients.

Establishing the efficacy of NSAIDs is important in view of recent concerns about potential adverse events with these drugs.[3–5] Although lumbar spinal manipulative therapy is also associated with adverse events,[6] the main concern is that manipulative therapy often requires referral by the general medical practitioner (GP) and additional expense for the patient.

Our aim was to investigate if the addition of diclofenac or a course of spinal manipulative therapy, or both, in patients with acute low back pain results in shorter recovery times in patients receiving recommended first-line treatment.

Methods

Patients

All patients with low back pain (with or without leg pain) of less than 6 weeks duration presenting to any of 40 participating GPs in Sydney, Australia, were invited to participate. The inclusion criterion was a complaint of pain in the area between the 12th rib and buttock crease causing moderate pain and moderate disability (measured by adaptations of items 7 and 8 of SF-36[7]). Exclusion criteria were: present episode of pain not preceded by a pain-free period of at least 1 month, in which care was not provided; known or suspected serious spinal pathology; nerve root compromise (with at least two of these signs: myotomal weakness, dermatomal sensory loss, or hyporeflexia of the lower limb reflexes); presently taking NSAIDs or undergoing spinal manipulation; any spinal surgery within the preceding 6 months; and contraindication to paracetamol, diclofenac, or spinal manipulative therapy.

Participating GPs screened all patients with low back pain according to eligibility criteria. All patients who met the criteria were given paracetamol 1 g to be taken four times daily and were given advice by the GP. Patients were asked to take paracetamol until recovery, or for a maximum of 4 weeks. A researcher met the patient

within 2 days (excluding Sundays) of seeing their GP to collect baseline data and randomise the patient to a treatment arm. A follow-up visit to the GP to monitor recovery and reinforce the advice was scheduled for 1 week after the initial visit. A further follow-up visit was scheduled if the GP believed it necessary. All patients signed an informed-consent form before participating in the study. The study protocol was approved by the University of Sydney Human Ethics Committee.

Procedures

A statistician not involved in data collection or analysis developed a randomisation schedule and produced 240 consecutively numbered sealed opaque envelopes containing each participant's allocation. Randomisation was done with randomly permuted blocks of 4, 8, and 12. Immediately after collecting baseline data the blinded researcher opened the allocation envelope, which contained a bottle of diclofenac or placebo drug, and gave this bottle to the patient. Active and placebo bottles were identically labelled. Patients were instructed to take their assigned treatment in addition to the paracetamol previously supplied by the GP. The randomisation envelope also contained a second envelope with the participant's allocation to active or placebo spinal manipulative therapy. This envelope was given to the treating physiotherapist to open in private. Therefore all participants were allocated to one of four groups: control group (placebo drug and placebo spinal manipulative therapy); NSAIDs group (diclofenac and placebo spinal manipulation); spinal manipulative therapy group (placebo drug and active spinal manipulative therapy); and spinal manipulative therapy and NSAIDs group (diclofenac and active spinal manipulative therapy).

Participants were instructed to take their assigned drug twice daily until the patient had recovered or for a maximum of 4 weeks. Placebo tablets were manufactured in the Faculty of Pharmacy of the University of Sydney, Sydney, Australia, and were identical to active diclofenac in shape, size, and colour—thus neither the blinded researcher nor participant could differentiate between the active and placebo treatments.

Spinal manipulative therapy was done by 15 physiotherapists, in 13 private clinics in Sydney, who had a minimum qualification of a graduate diploma in manipulative therapy, and who regularly used spinal manipulative therapy in their clinical practice. Participants allocated to spinal manipulative therapy had treatment two or three times per week (at the physiotherapist's discretion) to a maximum of 12 treatments over 4 weeks. If the participant recovered before the end of the 4 weeks, spinal manipulative therapy was stopped. Patients had spinal manipulative therapy according to a treatment algorithm developed by the researchers on the basis of views of expert clinicians and researchers.[8–10] The algorithm permitted the use of mobilisation or high velocity thrust procedures, which aimed to produce motion at the joints of the lumbar spine, thoracic spine, sacroiliac joint, pelvis, and hip.

Consistent with contemporary best clinical practice, the therapist adjusted the treatment to the clinical presentation of the patient rather than applying the same treatment to all patients. A full description of the spinal manipulative therapy protocol has been published previously.[11]

The placebo manipulative therapy was detuned pulsed ultrasound, which matched the treatment duration and patient's contact with the therapist with active spinal manipulative therapy. Active and placebo manipulative therapy sessions were matched in time (30–40 minutes for the initial session and about 20 minutes for follow-up sessions).[12] A researcher not involved in data collection or analysis audited the physiotherapy treatments (active and placebo) to ensure ongoing compliance with the protocol. Treatment credibility was assessed 1 week after starting the intervention with the 24-point Treatment Credibility Scale.[13] Participants were asked not to seek other treatments for their low back pain during the intervention and follow-up period. A record of additional treatments was kept for any patients who took other treatments within this time.

The primary outcome was the number of days to recovery, with recovery counted in two ways: (1) the first pain-free day (pain score 0 or 1); and (2) the first of 7 consecutive days in which the patient had a pain score of 0 or 1 out of 10.[14] To ensure a precise estimate of the time to recovery, participants completed a daily pain diary. To reduce potential for lost data, pain scores from the

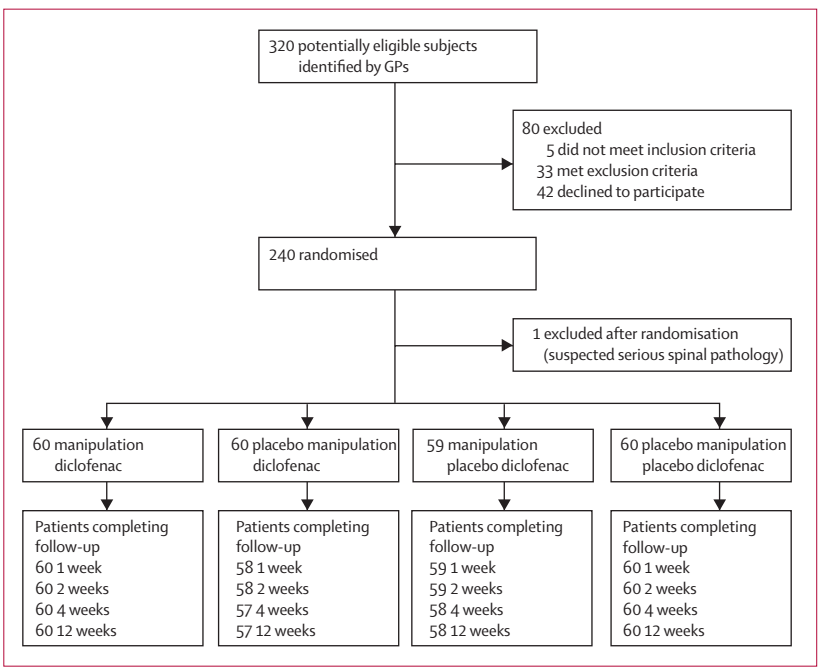


***Figure 1*: Trial profile**

Patients who did not complete follow-up were contacted by telephone and at this time they stated that they wished to withdraw from the study and provided no further data.

diaries were transcribed by the researcher at each of the follow-up telephone conversations.

Secondary outcomes were pain (pain score of 0–10),[14] function (10-point Patient Specific Functional Scale),[15] disability (24-point Roland Morris Disability Questionnaire),[16] and overall perceived effect.[17] Secondary outcomes were recorded at baseline, 1, 2, 4, and 12 weeks.

Adherence to spinal manipulative therapy was recorded by the treating physiotherapist and expressed as the proportion of planned sessions completed. Compliance with study medications was assessed by asking the patients to estimate their compliance as a percentage of the planned dose of paracetamol or diclofenac, and by collecting unused medications.

If participants reported any possible side-effects during follow-up visits with the GP or during phone follow-ups with open ended questioning, details were recorded. Outcome measures were recorded by a researcher masked to group allocation at 1, 2, 4, and 12 weeks. If patients had not recovered by 4 weeks then additional telephone follow-ups were done every 2 weeks until recovery or for a maximum of 3 months.

Statistical analysis

Study sample size was calculated with ACCorD software Version 1. We calculated that a sample size of 240 participants gave 80% power to detect a 20% difference in recovery rates between the control and intervention groups with an α level of 0·05. These calculations were based on a 50% recovery rate in the control group by 3 months. The study allowed for up to 10% of patients to drop out. All data were double entered and analysed by intention to treat. For primary outcomes, we deemed $p<0·05$ to be significant. For the secondary outcomes we deemed $p<0·01$ to be significant.

For the primary outcome of days to recovery we compared Kaplan-Meier survival curves with the log-rank statistic. Cox regression was done to estimate the effects of treatment group on risk of recovery. Secondary Cox regression analyses including three potentially important covariates (baseline pain, number of days in this episode, and number of previous episodes) gave very similar hazard ratios so the results of the Cox regressions without covariates only are given. The median days to recovery for each group was calculated. The proportional hazards assumption was tested using the time-dependent covariate method (p values ranged from 0·441 to 0·573).[18]

For secondary outcomes we estimated effects of diclofenac or spinal manipulative therapy on pain, disability, function, and overall perceived effect at 1, 2, 4, and 12 weeks with linear models. Baseline values of the dependent variable, number of days in this episode, and number of previous episodes were modelled. This trial is registered with the Australian Clinical Trials Registry, number ACTRN012605000036617.

Role of the funding source

The sponsor of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and the corresponding author had final responsibility to submit for publication.

Results

240 patients were recruited by 19 GPs from 14 general practices between June 2005 and October 2006 (figure 1). The general practices were located across a full range of socioeconomic areas, representative of an urban population. One participant was excluded after randomisation but before having any treatment because the physiotherapist and referring GP both were concerned that the patient had serious infection as the cause of their low back pain. An experienced clinical researcher not involved in the trial reviewed the case and recommended the participant be withdrawn from the trial and referred to a specialist for further examination. This individual was therefore excluded from the analyses. Review of treatment records identified five participants who did not have the correct spinal manipulative therapy intervention as allocated. 237 patients (99%) either recovered or were censored 12 weeks after randomisation.

Table 1 shows baseline demographic and clinical characteristics of patients. Participants had moderate baseline pain, moderate disability, and low fear avoidance. All participants started the interventions within 2 days of seeing the GP (excluding Sundays). No patients were defined as recovered before having

	Diclofenac	Placebo diclofenac	Spinal manipulation	Placebo manipulation	All participants
Age	39·5 (15·8)	41·9 (15·5)	41·4 (15·4)	40·0 (15·9)	40·7 (15·6)
Sex	50 (42%)	55 (46%)	55 (46%)	50 (42%)	105 (44%)
Duration of current symptoms (days)	9·2 (9·3)	9·1 (9·4)	9·0 (9·6)	9·2 (9·0)	9·13 (9·31)
Number of previous episodes	4·2 (7·3)	3·2 (5·3)	4·3 (7·6)	3·0 (4·9)	3·7 (6·4)
Disability*	13·4 (5·2)	12·9 (5·5)	13·8 (5·0)	12·5 (5·6)	13·1 (5·4)
Function†	3·9 (1·7)	3·9 (1·8)	3·8 (1·6)	4·0 (1·9)	3·9 (1·8)
Pain‡	6·4 (1·7)	6·6 (1·7)	6·7 (1·6)	6·3 (1·8)	6·5 (1·7)
PRSS-coping	3·6 (0·8)	3·5 (0·8)	3·5 (0·8)	3·7 (0·8)	3·56 (0·78)
PRSS-catastrophising	1·9 (1·0)	1·8 (0·9)	1·8 (0·9)	1·9 (1·0)	1·85 (0·94)
FABQ—work subscale	15·5 (10·4)	13·5 (10·3)	14·7 (10·5)	14·3 (10·3)	14·5 (10·4)
FABQ—activity subscale	17·3 (5·4)	16·7 (5·3)	17·2 (5·0)	16·7 (5·7)	17·0 (5·4)

Data are mean (SD) or number female (%). PRSS-coping=pain-related self statement scale–coping; scored from 0 (poor coping strategies) to 5 (strong coping strategies). PRSS-catastrophising=pain-related self statement scale–catastrophising: 0 (low catastrophising) to 5 (high catastrophising). FABQ-work=fear avoidance beliefs questionnaire–work; scored from 0 (no fear avoidance beliefs) to 42 (high fear avoidance beliefs). FABQ-activity=fear avoidance beliefs questionnaire–physical activity; scored from 0 (no fear avoidance beliefs) to 24 (high fear avoidance beliefs). *Roland Morris Disability Questionnaire; scored from 0 (no disability) to 24 (high disability). †Patient Specific Functional Scale; from 0 (unable to perform activity) to 10 (able to perform activity at pre-injury level). ‡Numerical pain rating scale, from 0 (no pain) to 10 (worst pain possible).

Table 1: **Baseline characteristics of participants**

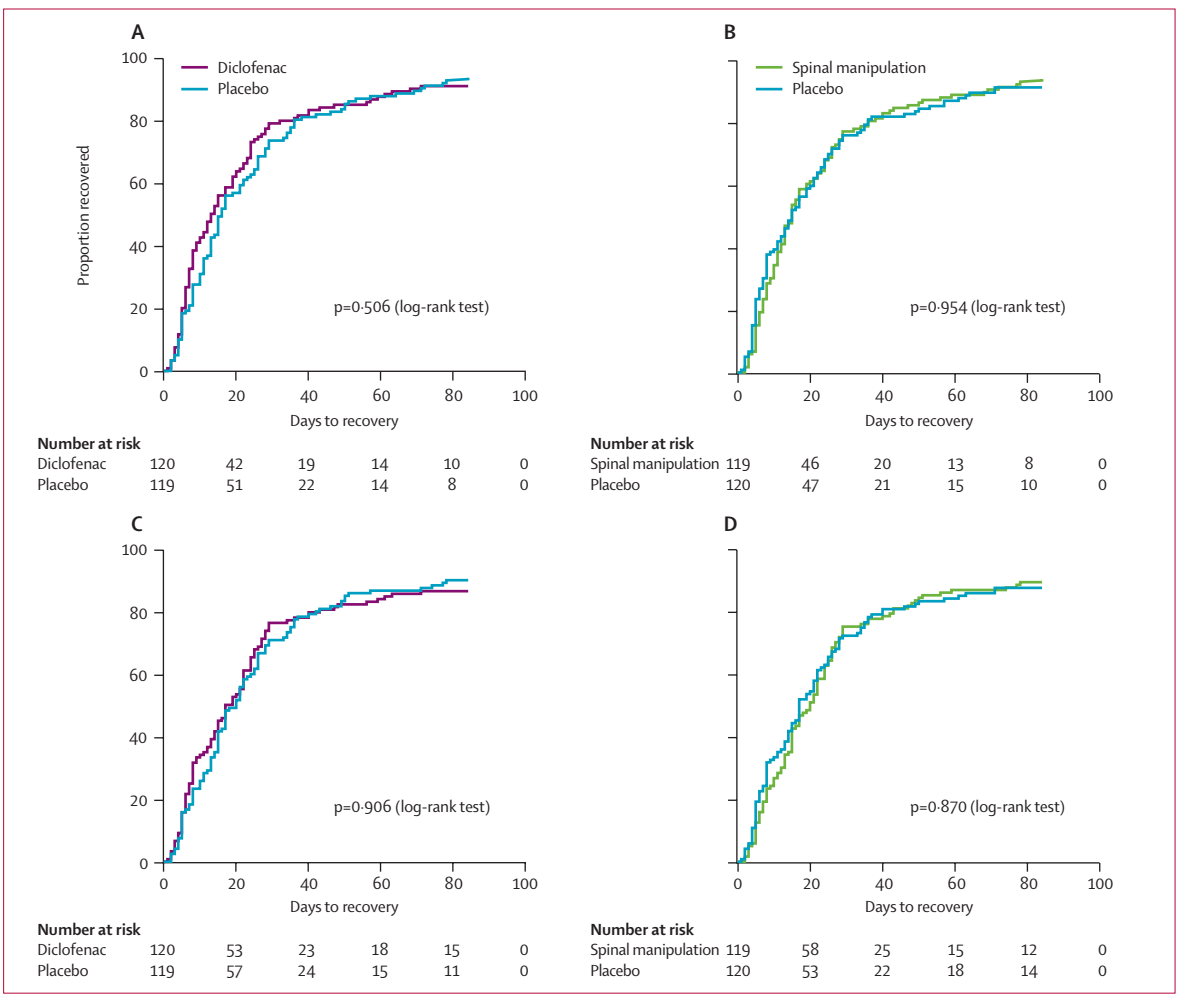
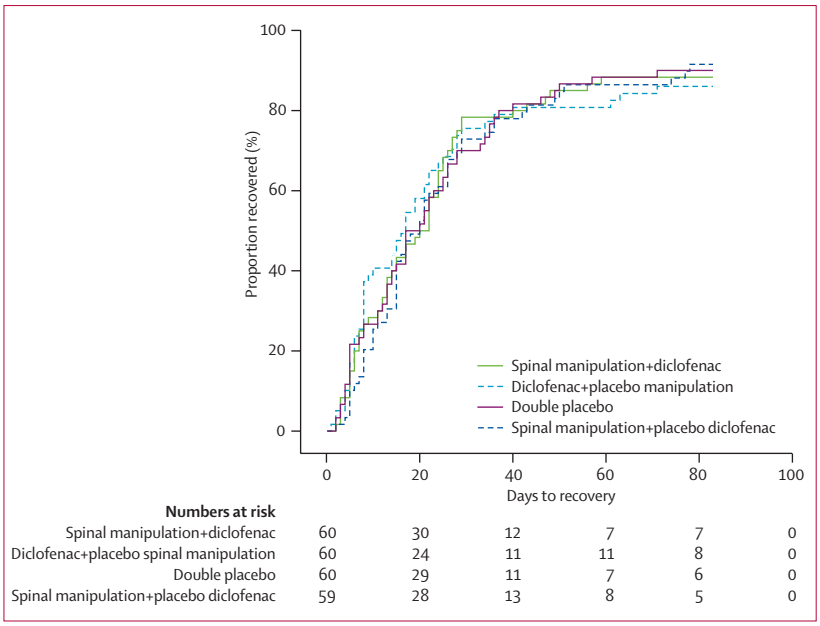


Figure 2: **Survival curves for days to recovery from low back pain**
(A) Diclofenac *vs* placebo; (B) spinal manipulation *vs* placebo; (C) diclofenac *vs* placebo; and (D) spinal manipulation *vs* placebo. In (A) and (B) recovery is defined as a pain score of 0 or 1 for one day and in (C) and (D) recovery is defined as a pain score of 0 or 1 for 7 consecutive days.

interventions. All patients saw the GP once before randomisation and were given advice and paracetamol. 115 patients (48%) attended at least one follow-up consultation with the GP and 62 (26%) had 2 follow-up appointments. 95 patients (40%) returned their unused paracetamol and a further 136 (57%) provided a verbal estimate of the percentage of prescribed dose taken. On the basis of these data we estimated that patients typically took about two-thirds of the prescribed dose of paracetamol (mean=68%, SD 37%). 87% (202/231) of patients took at least 25% of the prescribed dose of paracetamol, 72% (116/231) took 50% of the dose, and 48% (112/231) took 75% of the dose. Compliance with paracetamol across the four groups was not significantly different (p=0·224).

108 patients (45%) returned their unused diclofenac tablets and a further 126 (53%) gave a verbal assessment of the percentage of prescribed dose taken. On the basis of these data patients took a mean of 72·2% (SD 35·8%) of the prescribed dose. The mean percentage of full dose taken by the active diclofenac group (69·3% [33·8%]) and placebo group (75·0% [37·7%]) were not significantly different (p=0·225). 87% (202/234) of patients took at least 25% of the prescribed dose of diclofenac, 79% (185/234) took 50% of the dose, and 54% (127/234) took 75% of the dose.

The median number of spinal manipulative therapy sessions per week was 2·3 (IQR 1·5–3·0) for all patients. Median number of sessions per week for the active manipulative therapy group was 2·3 (1·5–3·0) and was 2·3 (1·5–3·0) for the placebo manipulative therapy group. Most participants had several low-velocity mobilisation techniques (232/239, 97%) with a small proportion also having high-velocity thrust techniques (12/239, 5%). 28 patients took additional cointerventions during the study period. The number of patients taking additional interventions was similar between the diclofenac (n=14; 12%) and placebo groups (n=14; 12%) and between the active (n=11; 9%) and placebo manipulative therapy groups (n=17; 14%).



Numbers at risk						
Spinal manipulation+diclofenac	60	30	12	7	7	0
Diclofenac+placebo spinal manipulation	60	24	11	11	8	0
Double placebo	60	29	11	7	6	0
Spinal manipulation+placebo diclofenac	59	28	13	8	5	0

Figure 3: **Survival curves for days to recovery from low back pain**
Recovery is defined as a pain score of 0 or 1 for 7 consecutive days.

	Diclofenac	p value	Manipulation	p value
Pain*				
1 week	−0·2 (-0·7 to 0·3)	0·488	0·2 (-0·3 to 0·7)	0·446
2 weeks	−0·1 (-0·7 to 0·4)	0·668	−0·4 (-1·0 to 0·1)	0·119
4 weeks	−0·1 (-0·6 to 0·4)	0·723	−0·2 (-0·7 to 0·3)	0·457
12 weeks	0·0 (-0·5 to 0·4)	0·892	−0·2 (-0·7 to 0·3)	0·373
Disability†				
1 week	0·5 (-0·8 to 1·8)	0·456	−0·7 (-2·1 to 0·6)	0·260
2 weeks	−0·6 (-1·9 to 0·8)	0·408	−1·4 (-2·7 to -0·1)	0·041
4 weeks	−0·7 (-1·8 to 0·4)	0·203	−1·0 (-2·1 to 0·1)	0·077
12 weeks	−0·1 (-1·3 to 1·1)	0·916	−0·5 (-1·7 to 0·7)	0·425
Function‡				
1 week	0·1 (-0·4 to 0·7)	0·674	0·1 (-0·5 to 0·7)	0·740
2 weeks	0·2 (-0·4 to 0·7)	0·575	0·4 (-0·2 to 0·9)	0·173
4 weeks	0·2 (-0·3 to 0·6)	0·477	0·4 (-0·1 to 0·8)	0·096
12 weeks	0·0 (-0·4 to 0·4)	0·955	0·1 (-0·3 to 0·6)	0·514
Global perceived effect§				
1 week	−0·3 (-0·7 to 0·2)	0·253	−0·1 (-0·5 to 0·4)	0·728
2 weeks	0·1 (-0·3 to 0·6)	0·506	0·4 (0·0 to 0·8)	0·06
4 weeks	0·0 (-0·3 to 0·3)	0·921	0·2 (-0·1 to 0·6)	0·156
12 weeks	0·1 (-0·3 to 0·4)	0·769	0·3 (-0·1 to 0·6)	0·158

Effect sizes (95% CI) for diclofenac and manipulation were adjusted for baseline values of the dependent variable, number of days in this episode, and number of previous episodes. 0=unchanged. For pain and disability negative values favour the active treatment, and for function and global perceived effect positive values favour the active treatment. *Pain measured with Numerical Pain Rating scale from 0 (no pain) to 10 (worst pain possible). †Disability measured with Roland Morris Disability Questionnaire from 0 (no disability) to 24 (high disability). ‡Function measured with Patient-Specific Functional Scale from 0 (unable to perform activity) to 10 (able to perform activity at pre-injury level). §Overall perceived effect scale from −5 (much worse) to 5 (completely recovered).

Table 2: **Effects of diclofenac or manipulation on secondary outcomes**

Treatment credibility was high for patients in all four groups. Mean credibility scores for active and inactive diclofenac groups were 18·5 (SD 4·7) and 17·3 (5·7) and for active and inactive manipulative therapy were 18·6 (4·5) and 17·1 (5·9) on a 0–24 point scale. 22 (9%) patients reported a possible adverse reaction to medication including gastrointestinal disturbances, dizziness, and heart palpitations. 11 adverse reactions were seen in participants taking active diclofenac treatment and 11 in participants taking placebo. One patient taking active diclofenac treatment experienced a suspected hypersensitivity reaction and ceased treatment. No participants reported serious adverse reactions associated with spinal manipulative therapy.

Participants who took active diclofenac did not recover more quickly than those who took placebo for either of the two recovery measures (log rank p=0·506, p=0·906). Because the efficacy of diclofenac did not seem to depend on how recovery was defined, hazard ratios and median days to recovery are only presented for recovery defined as the first day a patient obtained a pain score of 0 or 1. The hazard ratio for those taking diclofenac compared with those taking placebo was 1·09 (95% CI 0·84–1·42). Figure 2 presents the Kaplan-Meier recovery curves for patients taking diclofenac compared with those taking placebo diclofenac. Median days to recovery was 13 (95% CI 10–16) for patients taking diclofenac and 16 (95% CI 14–18) for patients taking placebo diclofenac.

Participants who had active spinal manipulative therapy did not recover more quickly than those who had placebo spinal manipulative therapy for either of the two recovery measures (log rank p=0·954, p=0·870). Because the efficacy of spinal manipulative therapy did not seem to depend on how recovery was defined, hazard ratios and median days to recovery only are presented for recovery defined as the first day a patient obtained a pain score of 0 or 1. The hazard ratio for those who had active manipulative therapy compared with those receiving placebo manipulative therapy was 1·01 (95% CI 0·77–1·31). Figure 2 shows the Kaplan-Meier recovery curves for patients assigned spinal manipulative therapy compared with placebo manipulative therapy. Median days to recovery was 15 (95% CI 13–18) for patients assigned spinal manipulative therapy and 15 (95% CI 12–19) for patients assigned placebo manipulative therapy.

The effects of NSAIDs and spinal manipulative therapy did not interact significantly (figure 3, p=0·625). The combination of diclofenac and spinal manipulative therapy (*vs* double placebo) did not appreciably shorten time to recovery (hazard ratio 1·10, 95% CI 0·76–1·60, p=0·609).

Neither diclofenac nor spinal manipulative therapy had a statistically significant effect on the secondary outcomes of pain, disability, function, or global perceived effect at any time point (table 2).

Discussion

Neither diclofenac nor spinal manipulative therapy gave clinically useful effects on the primary outcome of time to recovery. Findings from the secondary analyses support the primary analyses, showing no significant effects on pain, disability, or global perceived effect at 1, 2, 4, or 12 weeks, when diclofenac or spinal manipulative therapy, or both, were added to baseline care.

Both NSAIDs and spinal manipulative therapy have been shown to have small beneficial effects in patients with acute low back pain.[19,20] However, patients in these studies were not given advice and paracetamol as per standard guidelines. We can reasonably assume that when quality baseline care is provided, previously effective treatments might no longer provide additional benefit. A systematic review concluded that different types of NSAIDs are equally effective for acute low back pain,[21] which suggests that the results from our trial with diclofenac could be generalised to other NSAIDs.

The spinal manipulative therapy given in this trial included a range of low-velocity mobilisation and high-velocity manipulation techniques done by physiotherapists with postgraduate training in manipulative therapy. A systematic review of spinal manipulation concluded that there is no evidence that high-velocity spinal manipulation is more effective than low-velocity spinal mobilisation, or that the profession of the manipulator affects the effectiveness of treatment.[20] At present the active agent in spinal manipulative therapy and the mechanism of action of such treatment are unclear. Development of more effective types and doses of spinal manipulative therapy might be possible once the active agent and mechanism of action are known.

Our study provides rigorous evidence of the effects of adding diclofenac or spinal manipulative therapy, or both, to care based on international guidelines (advice and paracetamol) for patients with acute non-specific low back pain. A small number of patients (28/239) had cointerventions during the study period, which could have affected the results. The number of people taking cointerventions was similar in the active and placebo arms. Compliance rates, although not perfect, were high for both interventions and are representative of clinical practice. We do not believe that cointerventions or compliance had any significant effect on our results.

These results are important because both diclofenac and spinal manipulative therapy have potential risks and additional cost for patients. If patients have high rates of recovery with baseline care and no clinically worthwhile benefit from the addition of diclofenac or spinal manipulative therapy, then GPs can manage patients confidently without exposing them to increased risks and costs associated with NSAIDs or spinal manipulative therapy.

Contributors

All authors participated in trial design; MH, JL, MS, and JM participated in data collection; MH and CM analysed and interpreted the data; MH drafted the report; CM, JL, AM, CC, RD, MS, and JM critically reviewed the report; and CM, JL, AM, CC and RD obtained funding.

Conflict of interest statement

RD was a member of an advisory board about paracetamol for GlaxoSmithKline. Payments went to an audited hospital account for teaching and research purposes.

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