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RANDOMIZED TRIAL

Spinal High-Velocity Low Amplitude Manipulation in Acute Nonspecific Low Back Pain

A Double-Blinded Randomized Controlled Trial in Comparison With Diclofenac and Placebo

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Study Design. A randomized, double-blinded, placebo-controlled, parallel trial with 3 arms.

Objective. To investigate in acute nonspecific low back pain (LBP) the effectiveness of spinal high-velocity low-amplitude (HVLA) manipulation compared with the nonsteroidal anti-inflammatory drug diclofenac and with placebo.

Summary of Background Data. LBP is an important economical factor in all industrialized countries. Few studies have evaluated the effectiveness of spinal manipulation in comparison to nonsteroidal anti-inflammatory drugs or placebo regarding satisfaction and function of the patient, off-work time, and rescue medication.

Methods. A total of 101 patients with acute LBP (for <48 hr) were recruited from 5 outpatient practices, exclusion criteria were numerous and strict. The subjects were randomized to 3 groups: (1) spinal manipulation and placebo-diclofenac; (2) sham manipulation and diclofenac; (3) sham manipulation and placebo-diclofenac. Outcomes registered by a second and blinded investigator included self-rated physical disability, function (SF-12), off-work time, and rescue medication between baseline and 12 weeks after randomization.

Results. Thirty-seven subjects received spinal manipulation, 38 diclofenac, and 25 no active treatment. The placebo group with a high number of dropouts for unsustainable pain was closed praecox. Comparing the 2 active arms with the placebo group the intervention groups were significantly superior to the control group. Ninety subjects were analyzed in the collective intention to treat. Comparing the 2 intervention groups, the manipulation group was significantly better than the diclofenac group (Mann-Whitney test: $P = 0.0134$). No adverse effects or harm was registered.

Conclusion. In a subgroup of patients with acute nonspecific LBP, spinal manipulation was significantly better than nonsteroidal anti-inflammatory drug diclofenac and clinically superior to placebo.

Key words: acute nonspecific low back pain, spinal HVLA manipulation, randomized controlled trial, diclofenac, placebo-controlled. **Spine 2013;38:540–548**

Low back pain (LBP) is a common problem to medicine and a reasonable threat to all national health care systems. In 1998, total US health care expenditures for LBP were estimated at $90 billion.[1] Average total health expenditures for patients with back and neck problems increased from $4795 per year in 1997 to about $6096 per year in 2005, an inflation-adjusted increase of 65% (in 2005 US dollars).[2] Low back pain also incurs high indirect costs due to lost productivity.[3] Reducing ineffective treatments[4] is necessary to decrease the LBP associated costs.

The prevalence of LBP is estimated to be between 31% and 47%.[5–7] Statistically, women are affected more frequently than men; the level of education is important—patients with less education have a higher risk.[5] Subjects with osteoarthritis, vital exhaustion, depression, fear avoidance, or post-traumatic stress syndrome also seem to be affected more often.[8–15] On average, 80% of patients who receive treatment of acute LBP return to work within 1 month,[16] whereas approximately 7% develop chronic LBP.[6] However, those without treatment develop chronic LBP or recurrences in more than 60%.[17] Appropriate treatment therefore seems to be essential to avoid chronic pain.

Because of a multiple pathogenesis, there is not 1 single diagnosis of LBP. Today, just the rough differentiation between specific and nonspecific LBP is accepted. Structural lesions such as tumors, osteoporotic compression, or spondylolisthesis represent just 15% as specific diagnoses. Including degenerative processes (disc alterations, spinal stenosis, spondylarthrosis), 45% of the cases represent specific diagnoses. Thus, the

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The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.

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majority today still remain nonspecific, probably a mixture of different subgroups still to be defined.[18,19]

Recently, the direct costs of spinal disorders in Germany were calculated to be more than 9 billion a year.[20] However, the direct costs in industrialized countries are estimated to cover only 15% of the total expenditure including offwork and invalidity.[21] LBP ranks first, as cause for work disability and retains the third place as reason for early retirement.[22]

The treatment of LBP varies from medication with analgesics or nonsteroidal antiinflammatory drugs (NSAID), physical therapy up to different manipulation approaches,[23–26] none of the therapeutic approaches having a proven superiority compared with the others. Thus, today there is no clear-cut evidence-based recommendation for the treatment of acute nonspecific LBP.[23] To overcome this gap, the present study was initiated to compare, in patients with acute LBP, the effectiveness of spinal manipulation with the NSAID diclofenac, additionally placebo-controlled. Paracetamol analgesia was a rescue medication for all.

With respect to the relative risk of adverse effects of NSAIDs, diclofenac was chosen to be acceptable by using a restricted dose for a short period.[27]

The hypothesis for this trial was that treatment of acute LBP by spinal manipulation is equal or better than NSAID medication, and active intervention is more useful than rescue medication.

MATERIALS AND METHODS

Trial Design

This investigation was a double-blinded, randomized-controlled, clinical trial. In the first phase, it followed a 3-armed design, comparing fixed-dose diclofenac therapy, spinal high-velocity low-amplitude (HVLA) manipulation, and placebo. To ensure blinding, treatment was carried out in a double-dummy design consisting of placebo tablets in the spinal manipulation group and sham manipulation technique in the diclofenac group, or both, in the control group without active treatment. Because sham manipulation can be performed only in a single-blind manner, the clinical endpoints were assessed by a physician different than the one who performed the treatment and blinded to the treatment allocation of the subject.

Sample size calculation resulted in 52 intention-to-treat cases per group based on a relevant difference of 3.5 for the baseline corrected Roland-Morris Disability Score (RMS), a standard deviation computed from literature analysis of 5.4 and a power of 90%. After termination of the study, only 35 respectively 36 cases are available for the intention-to-treat analysis but the standard deviation is smaller (4.9), that is, the power would be 82% if calculated in the same manner as during study planning.

When 69 evaluable subjects had completed the study, an interim analysis was performed. This analysis showed statistically significant superiority of active compared with placebo treatment (Figure 2). Therefore, the placebo arm was closed for medical, ethical, and practical issues. The trial was continued comparing diclofenac with spinal manipulation only. The randomization code of the 2 active treatment groups had not been opened for the interim analysis. Double-dummy design again was used to ensure blinding.

Participants

The trial was conducted in 5 orthopedic or general practices in 4 different cities. These physicians elected the patients and performed the treatment according to randomization protocol. Four additional physicians acted as blinded investigators in nearby but not identical practices.

Inclusion criteria were patients of any sex between 18 and 55 years of age presenting with acute (for <48 hr before randomization) LBP, and written informed consent. Exclusion criteria were, known intolerace to NSAID or paracetamol, occurrence of LBP or spinal manipulation for any cause within the last 3 months, known or suspected abuse of alcohol or drugs, metabolic or malignant or any serious organic or neurological disease, atopic diathesis, any structural disturbances of the spine (osteoporosis, scoliosis, disc herniation, spondylolisthesis, hip dysplasia, and others). Women with childbearing potential had to undertake effective contraception. For real sham manipulation patients with dysfunction of the sacroiliac joint (SIJ) were excluded (by functional and pain-provocation tests). The design and all documents of the trial were approved by all involved regional ethics committees and all responsible authorities. The trial was performed according to the guidelines of Good Clinical Practice.[28]

INTERVENTIONS

After the patient presented in an outpatient practice with acute LBP complaint and after having given written informed consent, the patient was examined carefully for exclusion criteria according to the study protocol. A big number of patients had to be excluded or had refused to sign the informed consent. The number of patients not registered may be calculated as 5 times the subjects included. If eligible and after signing the informed consent the subject was randomized (using a phone call to the involved and responsible Institute of Biometrics) to spinal manipulation plus placebo tablets or to diclofenac 50 mg tablets 3 times a day plus sham manipulation, or to the placebo control group in which the subject received sham manipulation plus placebo tablets. During the second phase of the trial, the subjects were randomized to one of the active treatments only. All subjects were supplied with paracetamol 500 mg tablets to be taken whenever needed, but not more than 6 tablets a day. No other concomitant analgesic medication, acupuncture, or homeopathy was allowed.

To avoid too many variables as well as to receive consistent and clear evidence by the outcome, spinal manipulation was performed using the most popular segmental technique in Germany for the lumbar spine, almost identical to osteopathic HVLA manipulation (Figure 7A, B)[29]:

- The patient lies in the lateral recumbent position on the side without the identified segmental irritation with the physician standing at the side of the table facing the patient.

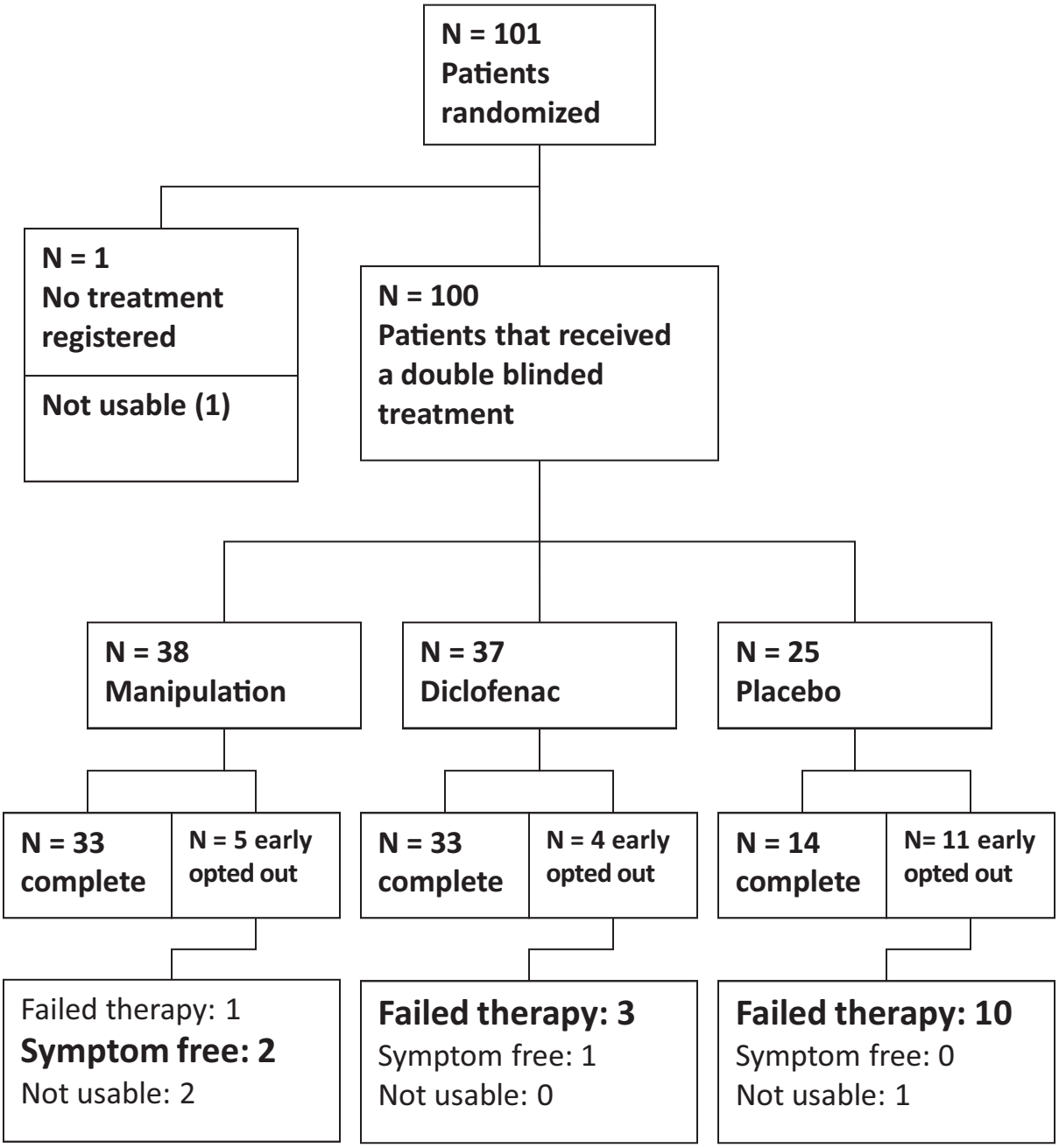

Figure 1. Flowchart of study patients who were recruited, randomized and treated, and who opted out the study.

- The physician palpates between the spinous processes of the dysfunctional segment and flexes the patient's upper leg at knee and hip until this segment opens in a neutral position of flexion. Extension has to be avoided.
- The lower leg can be flexed at hip and knee as much as necessary for the exact segmental positioning, but must stay secure on the table. The upper leg can reach as far over the table as necessary for a relaxed, but safe position of the patient on the table.
- While getting into a deep contact with 2 fingers of the caudad hand to the table-faced side of the upper spinous process of the identified dysfunctional segment, the physician places the cephalad hand in the antecubital fossa of the patient's upper arm while resting the forearm gently on the patient's upper lateral thorax directly below the shoulder.
- The physician's fingers of the caudad hand remain (Figure 7A) in deep contact with preliminary rotational tension on the spinous process while resting the forearm on the lateral pelvis, with the wrist building a "bridge."
- The patient's shoulder and pelvis (Figure 7B) are axially rotated in opposite directions. The patient inhales and exhales, and during exhalation, further rotational "slack" is taken up as a diagnostic probation mobilization to exclude contraindications against an impulse.
- With the patient relaxed and exhaling, the physician applies out of the rotational slack a HVLA thrust

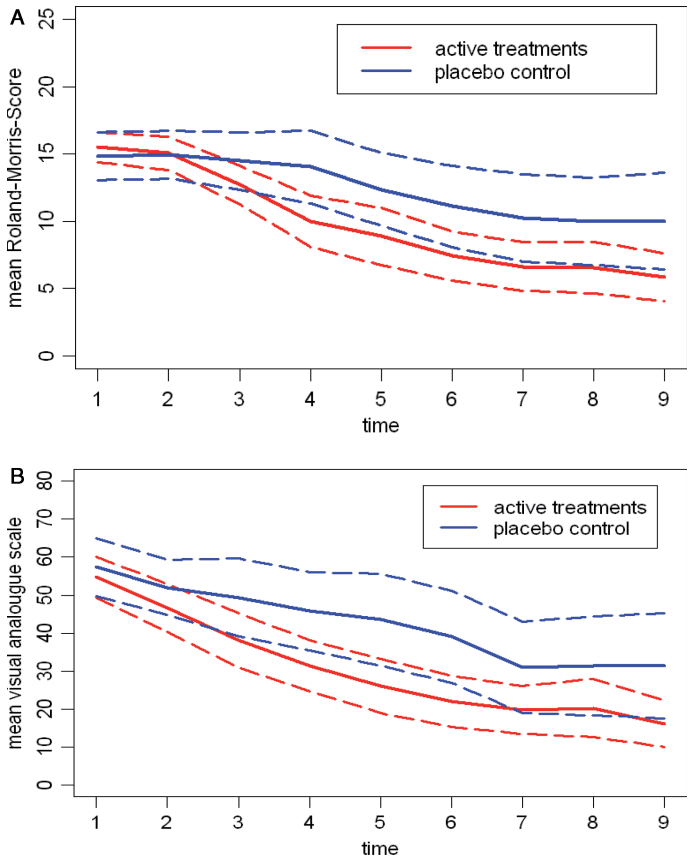

Figure 2. Interim results after 64 evaluable patients had completed the study. Depicted are mean values (continuous line) with borders of 95% confidence interval (dotted line) over time, starting from pretreatment values through days 7 to 9 after treatment. Blue indicates placebo control group (no active treatment, n = 22); red, both active treatment groups (n = 42), that is, spinal manipulation, or diclofenac. **(A)** Roland-Morris disability score (RMS); difference between treatment and control was statistically significant (P = 0.0034, 2-sided t test). **(B)** Visual analog scale (VAS) for pain.

simultaneously moving with his forearms the pelvis and sacrum towards him and the shoulder girdle into the opposite direction while pulling the upper spinous process of the dysfunctional segment upwards.

- The effectiveness of the technique has to be checked immediately according to the protocol. Eventually the technique has to be repeated.

Sham spine manipulation was performed using a HVLA manipulation to give the patient the same mechanical and acoustical sensations as are experienced during the *lege artis* manipulation, however, at an "incorrect" position. This technique is designed to treat the SIJ by traction on the leg combined with a cephalad impulse on the sacrum, which then remains neutral regarding the lumbar spine (Figure 8). In addition, this technique is applied on the opposite side of the identified segmental dysfunction. By using this procedure on a nondysfunctional SIJ, any influence to the lumbar dysfunction is avoided as well as any harm to the patient. The diagnostic and therapeutic techniques including the sham manipulation

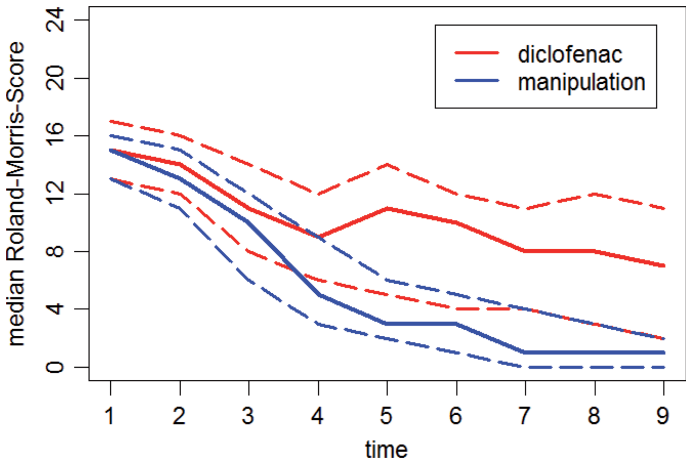

Figure 3. Median values (± 95% confidence interval [CI]) of the Roland-Morris Disability Score (RMS, primary variable) before treatment (day 1) and thereafter until the second investigation (days 7–9) in the collective intention to treat. Blue indicates manipulation; red, diclofenac; dotted lines, 95% CI.

were retaught in regular meetings of all investigators to keep the interindividual heterogeneity as small as possible.

Outcomes

Before treatment and between 7 and 9 days (as the follow-up was not terminated on weekend-days) after treatment, the subjects filled out questions and items in the personal diary and noted the intake of rescue medication. Three days after entrance in the trial, patients were seen again by a physician who treated them initially to undergo another spinal manipulation (according to treatment allocation) if necessary. Immediately thereafter, and at another time between days 7 and 9 after randomization, the patient was seen by another physician (blinded investigator). This physician was also well experienced in manual diagnostic techniques, but was not

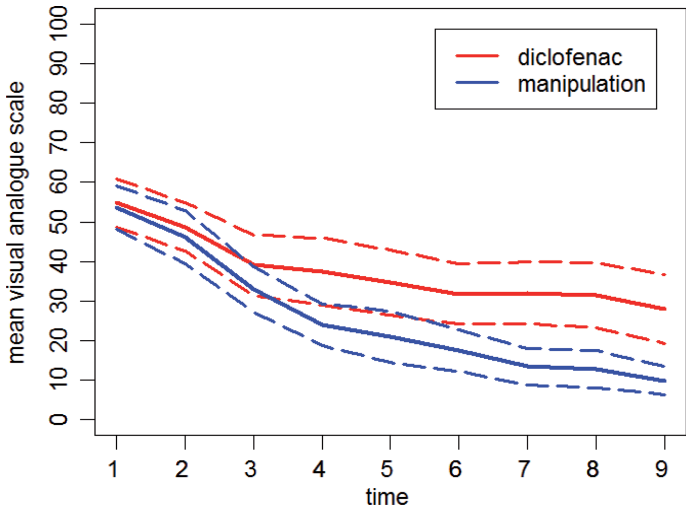

Figure 4. Mean values (± 95% confidence interval [CI]) of visual analogue scale (VAS) for pain before treatment (day 1) and thereafter up to the second investigation (days 7–9). Dotted lines indicate 95% CI.

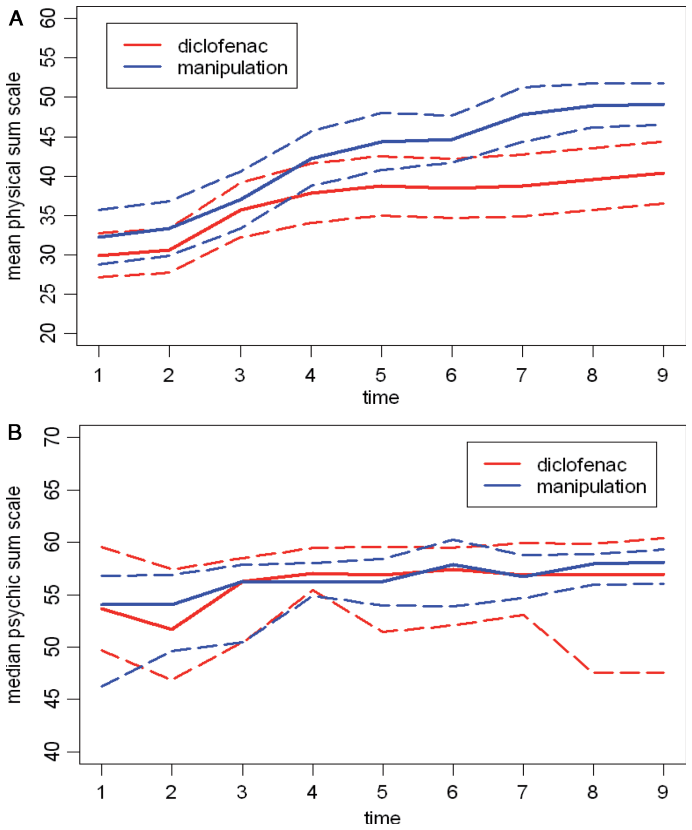

Figure 5. Mean values (± 95% confidence interval [CI]) of quality of life (SF-12 questionnaire) before treatment (day 1) and thereafter up to the second investigation (days 7–9). Dotted lines indicate 95% CI. **(A)** Physical sum scale. **(B)** Psychic sum scale.

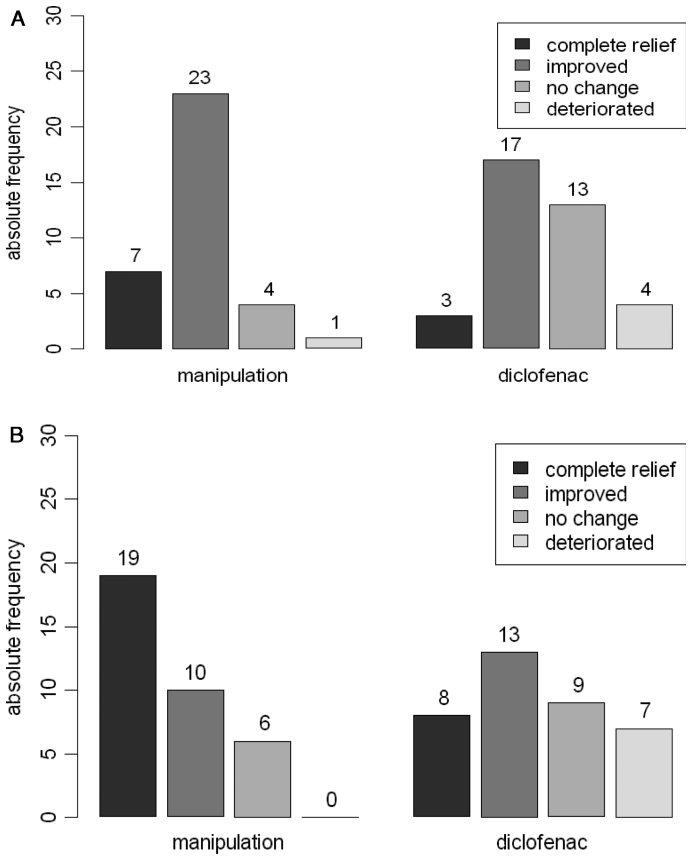

Figure 6. Comparison of the 2 active treatment groups with respect to the overall clinical impression of the blinded investigator's subjective impression of the patient. Given are absolute numbers of patients who were grouped as complete relief, improved, no change, or deteriorated. **(A)** Three days after treatment. **(B)** Seven to 9 days after treatment.

aware of the treatment allocation of the subject. Subjects who experienced persistence or intolerable aggravation of LBP were free to visit, any time, either the treating physician (up to day 3) or the blinded investigator (on days 4–7), to decide on continuation or termination of the trial to allow open therapy according to clinical standard.

The patient diary contained the RMS questionnaire, which is designed to assess self-rated physical disability caused by LBP and which is most sensitive for patients with mild to moderate disability due to acute, subacute, or chronic LBP, as the primary endpoint.[30,31] Secondary variables were 100 mm visual analogue scale (VAS) for self assessment of pain, quality of life questionnaire (SF-12), the global clinical impression of both the initially treating physician and the blinded investigator, the cumulative dose of rescue medication taken by the subject, number of days on which the subject took rescue medication, and off-work time (physician's certificate).

A 12-week follow-up was performed by phone interview, using the questions of the patient diary.

Randomization

A total of 210 folders were prepared and numbered from 1 to 210. To provide objective randomization the participating physicians electing the subjects initially received a pile of 30 of these numbered folders, 10 for each arm of the trial. The folders contained the personal diary for the patient and all forms for the first and the second physician. In addition, they received equally numbered boxes with the trial medication. The medication with diclofenac (50 mg) or placebo medication was prepared in an identical way so as to be not identifiable. With a new patient elected according to the inclusion and exclusion criteria and the patient having signed the informed consent the physician phoned the biometric institute giving the patients initials and date of birth. Only after that registration, the physician received the randomized number of the folder allocating the subject to one of the trial arms. By this means, the first physician could not pre-elect the subjects and thereby influence the results. Except for the last folder, it was not foreseeable what would be the random allocation of the next subject. Only 1 physician reached a total of more than 30 subjects. Therefore, this bias could be kept negligibly low.

Blinding

All subjects were completely blinded in respect to the randomized arm of the trial. All were touched and treated by the first physician with a standardized manual technique. The chosen technique of sham manipulation made it necessary to exclude any dysfunction of the SIJ, which in fact is often associated with LBP. This necessary step made it even

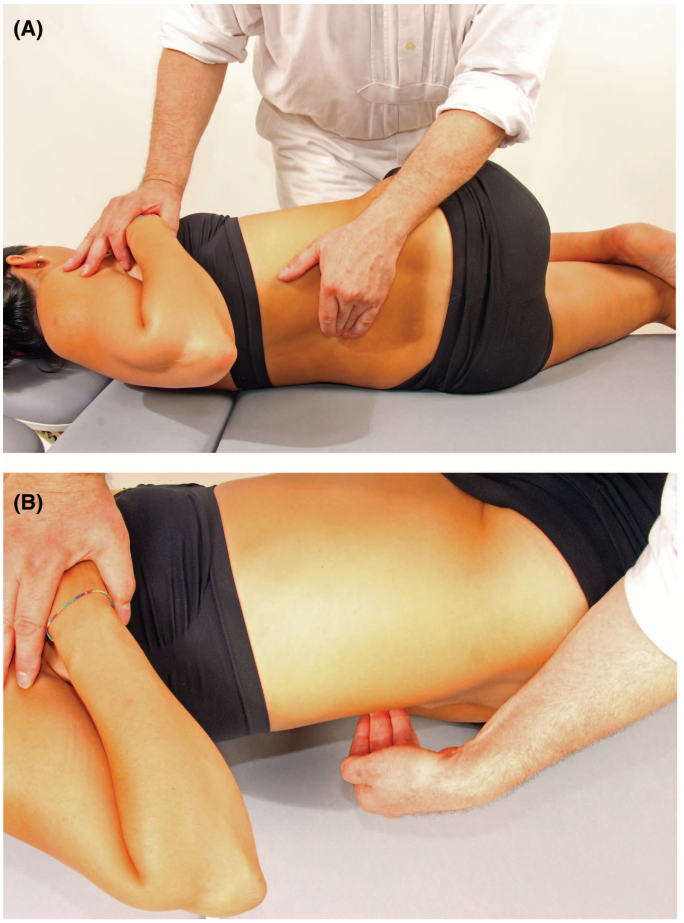

Figure 7. Position before high-velocity low-amplitude manipulation to lumbar spine. **(A)** View from the backside of patient. **(B)** position of physicians hand to guide the impulse to one spinous process. Reprinted with permission from the author.

more difficult to elect a high number of subjects. The rescue medication of paracetamol 500 mg was given in the original package.

The treating physician was obviously aware of using real HVLA manipulation on the lumbar spine or sham manipulation to the opposite SIJ. This could not be blinded.

Therefore, a second physician not aware of the random allocation sequence visited the subjects. This second physician investigated the results of the treatment not knowing which treatment the subject received. This second physician was not allowed to apply any treatment whatsoever before the termination of the trial.

Except for an unexpected early termination of the trial because of a patient experiencing persisting or aggravated unsustainable pain, there was no professional contact between the 2 physicians, with the nonmedical staff announcing the dates for the necessary 2 visits. By this double-dummy design, the double blinding was guaranteed.

Data Collection and Statistics

Because the interim analysis showed that active treatment was clearly superior to placebo (Figure 2A, B), the study was continued, as a consequence, as 2-armed study comprising active therapies only.

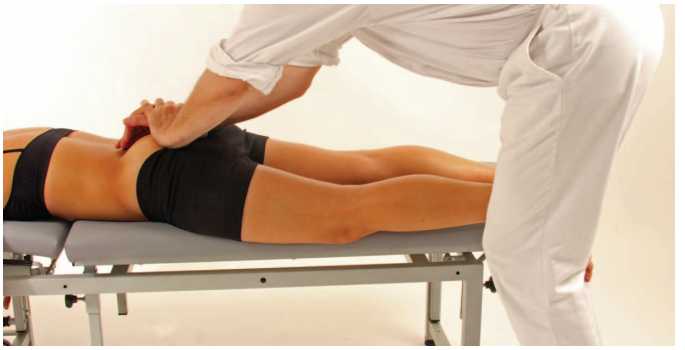

Figure 8. Position for sham-manipulation to the contralateral sacroiliac joint. Reprinted with permission from the author.

As a primary variable, the difference between the baseline value of RMS and the mean value of the post-treatment values was calculated. Other variables were calculated descriptively. Statistically significance was assessed by Student *t* tests and the Mann-Whitney test. In addition, 2-sided 95% confidence intervals were calculated for mean values, median, and the Hodges-Lehman estimator.

RESULTS

Analysis of Participants Flow and Numbers

A total of 101 patients were recruited for the trial: 69 during the initial 3-arm phase, and another 32 during the 2-arm phase. Because of protocol violation or missing data, not all subjects were evaluable. Altogether, 93 subjects were evaluable and formed the collective intention to treat, of whom 22 underwent placebo treatment, 36 received diclofenac, and 35 spinal manipulations (Figure 1). The subject characteristics are given in Table 1. There were no statistically significant differences between the groups indicating a balanced randomization.

Recruitment

The recruitment started on February 13, 2003, and the trial was ended on September 22, 2008. An interim analysis was executed in June 2006 as the rate of early terminations in the control group was relatively high. This arm of the trial was then closed and the recruitment continued just for the remaining 2 arms until September 2008.

The interim analysis in June 2006 compared the 2 treatment groups as a whole with placebo control. The analysis demonstrated statistically significant superiority of active treatment compared with placebo in the primary efficacy variable, RMS (Figure 2A), as well as in secondary variables like self-assessment of pain (Figure 2B), use of rescue medication or clinical judgment of the blinded investigating physician (data not shown). As a consequence, the placebo arm was closed. In the present article, therefore, the statistical calculation is focused on the direct comparison of the 2 active treatment groups.

TABLE 1. Demographic Data of the Collective Intention to Treat

Branch	Variable	Median Value	Standard Deviation	Min	Max
Manipulation (n = 38)	Age (yr)	34.14	9.45	18.00	55.00
	Height (cm)	176.11	7.59	163.00	195.00
	Weight (kg)	74.44	11.23	52.00	96.00
	Men (%)	63.89	62.16	…	…
	Baseline RMS	13.46	5.57	0.00	21.00
Diclofenac (n = 37)	Age (yr)	37.51	10.09	20.00	53.00
	Height (cm)	175.73	6.96	160.00	187.00
	Weight (kg)	74.41	12.86	55.00	105.00
	Men (%)	62.16	…	…	…
	Baseline RMS	14.42	4.80	2.00	24.00
Placebo (n = 25)	Age (yr)	39.25	10.23	22.00	55.00
	Height (cm)	176.54	9.51	162.00	194.00
	Weight (kg)	77.79	12.57	52.00	104.00
	Men (%)	54.17	…	…	…
	Baseline RMS	15.00	3.84	8.00	23.00

There was no statistically significant difference between the study arms (calculations not shown).

RMS indicates Roland-Morris disability scale score.

Baseline Data and Outcomes

The primary variable was the difference in RMS between baseline (before treatment) and mean values after treatment up to day 7 or 9. The medians of absolute values are presented in Figure 3. There was a clear difference between the treatment groups: the subjects with spinal manipulation showed a faster and quantitatively more distinct reduction in the RMS. The mean values (± SD) of the reduction *versus* pretreatment values were 7.71 ± 4.88 after spinal manipulation and 4.75 ± 4.93 in the NSAID group. The median value in the spinal manipulation group was 7.13, and in the NSAID group was 3.38. In addition the minimum in the spinal manipulation group was 0.00, whereas in the NSAID group −3.63, meaning an increase of pain. From all data, the difference was highly significant (Mann-Whitney test $P = 0.0134$). The 95% confidence interval (Hodges-Lehmann estimator) for the difference of baseline corrected RMS in both treatment groups is limited by 0.75 and 5.50, that is, excluding zero.

As a secondary outcome, the VAS for pain was analyzed showing a similar result as the RMS (Figure 4). Subjects noticed a faster and quantitatively more distinct reduction in this subjective estimation of pain after manipulation. A similar observation was made when comparing the somatic part of the SF-12 inventory (Figure 5A), indicating that the subjects experienced better quality of life after the spinal manipulation when compared to diclofenac. The median values of the psychological subscale of the SF-12 inventory (Figure 5B) did not differ between the 2 treatment groups.

The rescue medication was calculated both for the mean cumulative dose (numbers of 500 mg paracetamol tablets) and for the number of days on which rescue medication was taken by the subjects. Both values were numerically different: the cumulative dose was 2.22 ± 3.73 tablets and the number of days was 1.19 ± 1.77 after spinal manipulation. In the diclofenac arm, the patients on average took almost 3 times as many tablets (6.41 ± 10.67) and the number of days was almost twice as high 1.92 ± 2.61. However, because of a large interindividual variation, these differences were not statistically different. The off-work time was also numerically different, but without statistical significance: 1.24 ± 1.69 days after manipulation, 1.80 ± 2.10 days in the diclofenac arm.

In addition, the results of the physical examination of the blinded investigator collected at the first and second examinations were compared. These results concerning relief, improvement, no change, or deterioration are shown in Figure 6A for day 3 of the trial, and in Figure 6B for the final examination.

Harms

The safety analysis did not show any unexpected untoward events in either of the groups. Early termination due to treatment failure occurred in 10 of 22 subjects in the placebo group. In the spinal manipulation group, 1 of the 35 subjects opted out early because of treatment failure, and 2 refused further cooperation because of absence of complaints. In the diclofenac group 3 of the 35 subjects opted out early because of treatment failure, and 1 because of absence of complaints.

DISCUSSION

Limitations

The trial is limited to a subgroup of acute nonspecific LBP. Only subjects with no other health problems were included. The positive results of spinal manipulation may not be valid for patients with comorbidities such as osteoarthritis or osteoporosis of the spine, chronic LBP, obesity or for elderly patients.

The number of subjects included was not as high as expected, although the time of recruitment was extended for 5 years. The safety of the statement therefore decreases to 82%. One reason was the amount of exclusion criteria besides the expectation of the patient coming to the specialist for manipulation, mainly because of known adverse reactions to NSAIDs. It was also very difficult to convince the subjects to participate due to the prospect of potentially being in a placebo group. This possible preselection of patients may be seen as a point of weakness. Regarding the long time of recruitment a possible change of background conditions cannot be excluded, although there were no signs of that.

Regarding the manual intervention, only the most commonly used HVLA technique for this indication in many countries was investigated. The evidence of the study is therefore restricted to this technique, which, on the contrary, is part of the basic training of more than 57,000 US physicians as well as of 18,000 German physicians certified as manual medicine subspecialists. The implementation of all other manual techniques would have made it impossible to include enough subjects for acceptable evidence.

The follow-up was closed 12 weeks after randomization. This period may be too short to calculate the recurrence rate. As the trial included only acute LBP this short period was estimated to be sufficient.

Generalizability

The method of randomization as well as the blinding procedure were very efficient and can be generalized. The chosen sham manipulation in this trial is related to the real manipulation. Other trials to compare manual manipulation techniques should include other sham manipulations. To our knowledge, this is the very first trial with such a design.

Regarding the results, there was a magnitude of treatment effect itself compared with placebo (interim analysis) and a magnitude of superiority of manipulation compared with diclofenac. The consistent data of all variables measured (primary as well as secondary) fit nicely. The trial terminates with a very robust observation.

Interpretation and Recommendation

This is the first time that spinal manipulation was investigated in a double-blinded randomized controlled design showing clear superiority compared with placebo and NSAID. With the restrictions listed previously, HVLA manipulation can be recommended for the therapy for acute nonspecific LBP.

➢ Key Points

- ❑ Randomized controlled trial on acute nonspecific LBP.
- ❑ Comparison of spinal HVLA manipulation with diclofenac and rescue medication.
- ❑ A placebo group was closed for ethical reasons (pain).
- ❑ Final evaluation showed manipulation being significantly better than NSAID and clinically superior to placebo.

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The full protocol is accessible in German language at the Institute of Biometrics, Department of Mathematics of the University of Bremen, number KKS-HB.2002.I.D.01. Requests for a PDF version of the full protocol in German may also be sent to the author.

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