Year: 2010

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Number of text pages: 25

Number of figures: 1

Number of tables: 4

Supplementary Materials: 1 Table

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Abstract

Patients with acute lumbar disc prolapse with sciatica who are not considered candidates for surgery are usually treated with physiotherapy and non-steroidal anti-inflammatory agents. Moreover, the treatment with benzodiazepines is common practice in the absence of class I or II level of evidence. Here we assessed the role of benzodiazepines in the conservative management of acute lumbar disc prolapse.

Using a placebo-controlled, double-blinded design, 60 patients were randomized to receive placebo or diazepam in addition to mechanical physiotherapy and analgesics for the first seven days of conservative treatment of clinically and radiologically confirmed lumbar disc prolapse. The primary objective was to evaluate if physiotherapy plus analgesics, but without benzodiazepines, is equivalent to the same therapy plus benzodiazepines. The primary endpoint was centralization of referred pain at day 7.

Twenty-six female and 34 male patients were enrolled. The median age was 42 years (range 22-68 years). Analysis of the primary endpoint demonstrated equivalence between placebo and diazepam (median 60% versus 50% reduction of distance of referred pain at day 7) within the predefined equivalence tolerance of 20% at a significance level of $p<0.05$. Regarding the secondary endpoints, the median duration of the stay in hospital was shorter in the placebo arm (8 vs 10 days, $p=0.008$), and the probability of pain reduction on a visual analog scale by more than 50% was twice as high in placebo patients ($p<0.0015$). Benzodiazepines should not be used routinely in patients treated with mechanical physiotherapy for lumbar disc prolapse.

Key words: benzodiazepine, diazepam, lumbar disc prolapse, centralization, physiotherapy

Introduction

Lower back pain is one of the commonest diagnoses associated with sick leave and chronic disability. Most presumed standards of care have not been confirmed to effective in appropriate clinical trials (8-10, 26). A 2003 Cochrane review concluded that "muscle relaxants are effective in the management of non-specific low back pain, but the adverse effects require that they be used with caution" (27). Approximately 5% of the patients with lower back pain suffer from lumbar disc prolapses verified by neuroimaging (15). The conservative management of clinical symptoms and signs associated with lumbar disc prolapse includes rest, various strategies of physiotherapy and various medications, notably non-steroidal anti-inflammatory agents or low-to-medium potency opioids, and muscle relaxants, mostly benzodiazepines (7, 29). Because of their sedative effects and a potential for addiction, both opioids and benzodiazepines should only be used where they are clearly effective and indicated.

The first randomized trial that we identified did not demonstrate a superior outcome for patients with unspecific acute lower back pain treated with diazepam as opposed to placebo, but that study was performed more than 40 years ago, prior to the availability of computed tomography (CT) and magnetic resonance imaging (MRI) (16). A recent review (26) concluded that randomized trials had reported little efficacy of diazepam in acute unspecific lower back pain (23) and either no (5) or only minor benefits from benzodiazepines in patients with chronic unspecific lower back pain (4, 25). Only 20% of the conservatively treated patients received muscle relaxants in the US (29). This figure is probably higher in Europe.

Although there are almost no prospective studies on the impact of various approaches of physiotherapy on the symptoms and course of lumbar disc prolapse, physiotherapy is commonly prescribed in this patient population. We have confirmed active mechanical physiotherapy based on the pathophysiological concepts of centralization *versus* peripheralization of referred pain (12, 19, 21) to be feasible and acceptable to many patients

with lumbar disc prolapse (6). Peripheralization and centralization refer to changes in the projected area of radicular pain associated with lumbar disc prolapse. In a previous prospective phase II trial, centralization was found to be predictive of a favourable outcome in patients with lumbar disc prolapse (6).

Patients with low back pain and acute sciatica from lumbar disc prolapse usually exhibit an enhanced tone of the lumbar extensor muscles, a reduction of the physiological lumbar lordosis and a lateral shift of the vertebral column (3, 20, 28). The increased tone of the extensor muscles may not be a pathological response pattern, but may actually serve a protective function to prevent flexion of the spine and thus an increase of the prolapse. Some doubts therefore remain regarding the use of muscle relaxants in the acute phase of conservative treatment of this condition. The present trial sought to evaluate whether the outcome of conservative treatment of lumber disc prolapse with mechanical physiotherapy using repeated spinal movements in a preferred direction and analgesics, but without benzodiazepines, is equivalent to the same treatment plus benzodiazepines.

Methods

Patients

This prospective, randomized, placebo-controlled, double-blind trial (ClinicalTrials.gov ID NCT00533286) was approved by the Ethics Committee of University of Tübingen Medical School (53/2001). All participating patients gave written informed consent. The trial included patients who fulfilled the following inclusion criteria: age between 18 and 75 years, sciatica without or with neurological deficit attributable to lumbar disc prolapse, CT or MRI confirmation of lumbar disc prolapse, pain centralization within the first physical therapy session and informed consent. The length of the pain history was not specified in the inclusion criteria. Patients could not be enrolled if they had bladder or bowel disturbance or acute (< 24 h) development of paresis grade 1 or plegia (14) because these patients were considered candidates for surgery. Further, patients could not have had taken benzodiazepines for more than 2 weeks, any history of benzodiazepine intolerance, prior surgery for disc prolapse, or prior trauma to the vertebral column.

Study design

The patients were randomized after informed consent in the order of consenting using a computerized randomization list at the Medical Biometry Unit to receive placebo (2 tablets daily, arm A) or diazepam (2 x 5 mg) (arm B). This list contained numbers reflecting treatment A or B. This numbers were used to identify the bottles with separately manufactured study medication which matched placebo and diazepam in size, shape and color. This approach prevented the consenting physician from knowing the result of the randomization process by estimating from the preceeding patient. The bottle with study medication was stored at the ward and the medication was given to the patient on a daily basis. Patients, physiotherapists (DB, EM, SB) and the clinical neurologists (WW, MW) were blinded to treatment arm allocation. The medication was adjusted and gradually tapered from day 5 on by the treating physicians in cooperation with the principle investigator (MW). The

guidelines for tapering followed the general practice of our physicians to reduce diazepam doses depending on symptom reduction reported by the patient. The use of other muscle relaxants was not permitted. The treating physiotherapists, physicians and patients remained blinded throughout the study and the reports from the hospital did not disclose the study arm that the patient was allocated to. Mechanical physiotherapy was administered as extensively described (6) and diclofenac was used as the basic analgesic and anti-inflammatory agent. Its dose was adapted according to patients` needs and as deemed necessary by the treating physicians. Further analgesics were allowed according to the preference of the treating physicians. The extent of the lumbar disc prolapses on CT or MRI was assessed as previously described (6).

Endpoints and follow-up

The patients were documented at the day of study entry (day 1) and then at days 3, 5, 7, 9 and at the day of discharge from hospital. Follow-up examinations were scheduled at 6 weeks and at one year after discharge. The endpoints were planned to be assessed at day 7 compared with day 1. The following parameters were measured or documented (12, 24): centralization, impairment (disability scale), pain on a visual analog scale, duration of pain within 24 h, straight leg raise in angular degrees, quality and extension of sensory loss, muscle strength, and walking distance and mobility (finger floor distance). The primary endpoint was defined as the extent of reduction (centralization) of referred pain in percent at day 7 compared with day 1. The distance from the affected vertebral segment at the lower back to the area of most distal pain projection was measured in cm. Increases in pain projection were to be calculated as 0% reduction. Such patients would be considered candidates for surgery. In fact, only one patient of group A developed such a peripheralization of pain projection of 1 cm until day 7. Therefore, counting negative values not as 0% reduction, but actually as negative values might have been more correct theoretically, but did not alter the study results here (data not shown). Secondary endpoints were as follows: duration of inability to work after discharge measured in days as determined

by the local treating physicians, duration of stay in hospital, reduction of scores on the

Roland-Morris disability scale on day 7 compared with day 1, number of patients with: pain

reduction on the visual analog scale of 50% or more on day 7 compared with day 1; increase

in the straight leg raise by 50% or more; reduction of time (h) with pain by 50% or more;

changes of sensory loss; improved muscle strength by at least one grade; improvement of

finger floor distance; walking distance at day 7; consumption of study medication and of

diclofenac per D1-D7 (mg); request for further anagesics, and inability to work at 4 weeks

after discharge.

Statistics

Based on the sample size consideration 60 patients were included into the study. This was

calculated to be sufficient for proving the equivalence of the two therapies regarding the

centralization of the referred pain between study day 1 and 7 in percent with an equivalence

tolerance delta of 20% (alpha=5%, beta=10%). A clean file of the data was submitted to the

Institute for Medical Biometry at the University of Tübingen for the final analyses. Data

analyses were performed by C.E. with the statistical analysis software SAS (version 9.1.3,

SAS Institute Inc, Cary, NC, USA) based on the intention-to-treat population from which none

of the randomized patients had to be excluded. All endpoints were measured as changes

between study day 1 and 7 if not otherwise mentioned. Missing data were not replaced. The

primary endpoint was tested using the Mann-Whitney test of equivalence (30) because the

data were not normally distributed. The 95% confidence interval for the difference in the

primary endpoint between placebo and diazepam was calculated according to Altman and

colleagues (2). The normally distributed endpoint improvement of finger floor distance was

analyzed using Student's t-test. The U-Test was used for non-normally distributed continuous

endpoints (duration of inability to work, reduction of disability scores, walking distance at day

7, consumption of diclofenac and study medication, absolute duration of stay in hospital and

improvement of finger floor distance). The secondary endpoints reduction on the visual

analog scale of at least 50%, increase of the straight leg raise of at least 50%, reduction of

time with pain of at least 50%, improvement of muscle strength of at least one grade and inability to work at 4 weeks after discharge were analyzed using the Cochran-Mantel-Haenszel test for 2x2 tables and calculating risk ratios, the secondary endpoint change of reduction of sensory loss using a Fisher-Exact test. All secondary endpoints were analyzed in an explorative sense.

Results

Sixty patients were enrolled between August 2002 and March 2006. The median age was 42
years (range 22-68 years). A further 207 patients were screened for possible participation in
the trial, but were not included for the reasons summarized in the Supplementary Table,
chiefly because they did not meet the inclusion criteria (Fig. 1). The study population
consisted of 26 females and 34 males. Patient characteristics are summarized in Table 1.
The two patient groups were well-balanced for relevant clinical criteria. The neuroimaging
findings of 52 (24 placebo, 28 diazepam) patients, either CT (n=25; 15 placebo, 10
diazepam) or MRI (n=27; 9 placebo, 18 diazepam), were centrally re-reviewed by C.M. and
U.E. At their largest extension on CT or MRI, the sizes of the prolapses were $\leq$ 25% of the
spinal canal cross sectional plane in 29 patients (11 placebo, 18 diazepam), 25 – $\leq$ 50% in
11 patients (5 placebo, 6 diazepam), 50 – $\leq$ 75% in 7 patients (6 placebo, 1 diazepam), and
> 75% in 5 patients (2 placebo, 3 diazepam). Six patients had a foraminal prolapse (3
placebo, 3 diazepam). Sequestration was seen in 9 patients (5 placebo, 4 diazepam). Thus,
there was a higher frequency of large prolapses in the placebo group. Yet, there was no
obvious association of the extent of spinal canal narrowing by the prolapses with the
detection or grade of pareses. Data for the 7 day endpoints were collected for 58 patients
since 2 patients had surgery prior to day 7. Fifty-five patients (92%) attended the 6 weeks
appointment, 45 patients (75%) attended the one year appointment.

The median time on study medication was 5 days in the placebo and 5 days in the diazepam
arm. The median doses of study medication were 50 mg in both arms. The most important
treatment results are summarized in Tables 2 and 3. The primary endpoint defined as the
median centralization of referred pain at day 7 showed equivalence within the predefined
tolerance of equivalence of 20% between placebo (60%) and diazepam (50%) (p<0.05).
Specifically, this test sought to demonstrate that the median difference in favor of diazepam,
if any, is truly less than 20%. The observed difference was 10% in favor of placebo, and this
was indeed statistically different from a null hypothesis of 20% in favor of diazepam. The

result does not provide evidence for a complete absence of a difference, but the 95%
confidence interval for the differences in centralization in referred pain between placebo and
diazepam was -15% to 24%. This result is not fully congruent with the result of the
equivalence test, but if there may be a difference of more than 20%, it is in favor of placebo,
which also confirmes the primary hypothesis. Accordingly, we thus confirmed the primary
hypothesis that the conservative treatment used here without diazepam support is not inferior
to the same treatment with diazepam support. Moreover, the median duration of the stay in
hospital was shorter in the placebo arm (8 vs. 10 days, p=0.008), and the probability of pain
reduction on the visual analog scale by more than 50% was twice as high in placebo patients
(p=0.0015).

Most other secondary endpoints appeared to favor the placebo arm, too, although the
differences were not significant. This includes the median duration of inability to work after
discharge (15 vs. 26 days, p=0.73); the median reduction of scores on the Roland-Morris
disability scale on day 7 compared with day 1 (5 points reduction vs. 3 points, p=0.67); the
number of patients with reduction of sensory loss (63% vs. 50%, p=0.63); the median walking
distance at day 7 (1000 meters in both groups because 25 placebo patients and 19
diazepam patients reached 1000 m, but different ranges, p=0.07); the median consumption
of diclofenac per D1-D7 (750 mg in both groups but different ranges, p=0.78. Additionally
patients in the placebo group showed a 1.25-fold higher chance of a reduction of time (h)
with pain by 50% or more at day 7 compared with day 1 (p=0.26) and an improvement of
muscle strength by at least one grade (p=0.54) whereas patients in the diazepam group
showed a 1.3-fold risk of not being able to work at 4 weeks after discharge (p=0.43) and the
request for further analgesics in addition to diclofenac was 1.3-fold higher (p=0.36) (Table 4).
In contrast, there was a 1.2-fold higher chance for an increase in the straight leg raise by
50% or more in the diazepam arm (p=0.79) and the mean improvement of the finger floor
distance was higher in this group (6.2 cm vs 5.0 cm, p=0.75).

Six placebo patients and 7 diazepam patients had surgery within 6 weeks of study entry.

Overall seven placebo patients and 8 diazepam patients had surgery within one year of study

entry. The surgically treated patients usually had large or intraforaminal or sequestrated prolapses.

Twenty-two diazepam and 23 placebo patients were reevaluated at one year follow-up. Most parameters associated with the lumbar disc prolapses had improved in both treatment arms. No longterm effects of being assigned to either treatment arm became apparent. The rate of patients with pareses of any grade decreased from 54% (15 of 28 patients) to 14% (3 of 21 patients) in the diazepam group and from 66% (19 of 29 patients) to 13% (3 of 23 patients) in the placebo group. The rate of patients with sensory loss changed from 63% (19 of 30 patients) to 43% (9 of 21 patients) without improvement in the diazepam group and from 77% (23 of 30 patients) to 44% (10 of 23 patients) in the placebo group, respectively. The degree of impairment decreased from a median of 14.5 to a median of 1 point in the placebo group, and from 14 to 2 in the diazepam group.

Discussion

It is a common belief that muscle tension causes lower back pain. Accordingly, various measures assumed to reduce pathologically enhanced muscle tension including muscle relaxants, massages and physical applications have become part of the general therapeutic repertoire for patients with lower back pain (18) and specifically for patients with lumbar disc prolapse. The therapeutic efficacy of these measures has remained obscure.

Flexion of the vertebral column, the major contributor to lumbar disc stress, causes an anterior approximation of the vertebral bodies, a mechanical dislocation of the nucleus pulposus backwards and ultimately a lumbar disc prolapse associated with sciatica and neurological deficits attributable to root compression (1, 13). Experimental studies have indicated that porcine lumbar discs respond to damage induced by electrical stimulation with an increased tone of the erector trunci muscles (17). Accordingly, we hypothesized that the increased muscle tone in human patients with lumbar disc prolapses may serve the aim to prevent further flexion of the spine and further flexion-associated disc damage.

Our current standard approach of physiotherapy for these patients (6) aims at preventing a further dislocation of nucleus pulposus material and instead relieving the posterior annulus fibrosis from mechanical pressure. The concurrent use of benzodiazepines such as diazepam would not only weaken the natural protective response of increased muscle tone in the erector trunci muscle, but would also counteract this treatment strategy.

The results of the present prospective randomized trial questions the value of prescribing benzodiazepines in the first days of conservative treatment of sciatica associated with lumbar disc prolapse. We studied a well-characterized and deliberately enriched patient population not just suffering from unspecific lower back pain, but from sciatica attributable clinically to a defined lesion documented by neuroimaging. We excluded patients where we judged immediate surgery to be necessary, this is, patients with bladder or bowel disturbance or acute (< 24 h) development of paresis grade 1 or plegia (14). The patients enrolled in our trial were in principle all candidates for elective surgery because they had neurological symptoms

or signs or both attributable to a radiologically verified lesion. On the other hand, we (6) and others have made the experience that many of these patients can be managed with conservative treatment. In that regard, the rate of surgery of 13 of 60 patients within 6 weeks of study entry was not unexpected.

The patient characteristics in both study arms of the present study were well-balanced for all clinical parameters except for the higher frequency of larger disc prolapses in the placebo group (Table 1). Although one might hypothesize that this may have favored the diazepam group, there is indeed no evidence that the size of prolapses predicts outcome (22). The primary endpoint defined as centralization of referred pain at day 7 showed equivalence between placebo and diazepam at the dosing schedule used here within the defined equivalence tolerance. In retrospect, it might have been preferable to assess back and leg pain separately as outcome measures (11). Yet, the diazepam group did also not show superiority in any of several secondary endpoints evaluated at day 7 after the start of treatment (Tables 2 and 3). Moreover, the median duration of the stay in hospital was shorter in the placebo arm. We are aware that this endpoint is of minor significance since the patient population studied here is managed as out-patients in many countries throughout the world. Further, the probability of pain reduction on a visual analog scale by more than 50% was twice as high in placebo patients.

Admittedly, this study has some inherent weaknesses: we did not prove that muscle relaxation was truly achieved by the doses of diazepam used here and we cannot rule out that diazepam was underdosed or that sedative effects interfered with a possible effect that could be derived from the pharmacological effect of muscle relaxation. Of note, the follow-up data at one year do not suggest a longterm adverse effect of benzodiazepines either. Anyhow, our trial results allow to conclude that benzodiazepines should no longer be considered standard of care for the acute conservative treatment of sciatica associated with lumbar disc prolapse.

Acknowledgement

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Table 1. Patient characteristics.

	Placebo (A, n=30)	Diazepam (B, n=30)
Age (median, range)	42.5 (22-61)	43 (30-68)
Females (n, %)	15 (50%)	11 (37%)
Employed (n)	29	26
Unemployed (n)	1	4
Referred pain in cm (median, range)	89 (10-140)	83 (10-130)
Disability score (median, range) (24)	14.5 (7-22)	14.0 (6-24)
Pain on visual analog scale (median, range)	8 (3-10)	8 (3-10)
Straight leg raise in angular degrees (median, range)	45 (0-93)	38.5 (12-88)
Hours with pain on day 1 (median, range)	14.5 (3-24)	17.5 (3-24)
Sensory loss (n, %)	23 (76.6%)	19 (63.3%)
Paresis (n, %)	19 (63.3%)	15 (56.7%)
Missing data	*1*	*2*

Finger floor distance in cm (median, range)	40 (0-73)	36 (0-85)
Missing data		*2*
Walking distance in meters (median, range)	166 (2-1000)	150 (0-1000)
Missing data		*1*
Pain history in days (median range)	14 (2-180)	21 (1-300)
Acute pain (up to 90 days)	28	27
Chronic pain (more than 90 days)	2	3
Preexposure to analgesics (mainly diclofenac) within last 14 days (n, %)	24 (80%)	25 (83%)
Missing data	*4*	*2*
Preexposure to benzodiazepines within last 14 days (n, %)	7 (23%)	8 (27%)
Missing data	*4*	*3*
Lumbar disc prolapse $\leq$ 25% of the diameter of the spinal canal	11	18
Lumbar disc prolapse 25 - $\leq$ 50% of the diameter of the spinal canal	5	6
Lumbar disc prolapse 50 - $\leq$ 75% of the diameter of the spinal canal	6	1
Lumbar disc prolapse > 75% of the diameter of the spinal canal	2	3

Missing data	6	2

Location of prolapse between vertebral bodies:

lumbar 2 and 3	1	2
lumbar 3 and 4	2	1
lumbar 4 and 5	14	11
lumbar 5 and sacral 1	13	16

Table 2. Clinical trial endpoint results

Parameter	Trial arm	N	Median	Range	25% percentile	75% percentile	≥ median (%)	P value
Reduction of distance of referred pain at day 7[a] (in %)	Diazepam	29	50	0-100	20	78.9		<0.05
	Placebo	29	60	0-100	14.1	100		
Duration of inability to work in days[b]	Diazepam	29	26	0-87	7	42		0.73
	Placebo	29	15	0-82	7	41		
Reduction of disability at day 7[b]	Diazepam	29	3.0	0-15	3	7		0.67
	Placebo	29	5.0	3-14	1	8		
Walking distance at day seven in m[b]	Diazepam	29	1000	0-1000			66	0.07
	Placebo	29	1000	45-1000			86	

Diclofenac consumption up to day 7 in mg[b]	Diazepam	28	750	0-7200			61	0.78
	Placebo	29	750	0-1050			55	
Consumption of study medication up to day 7 in mg[b]	Diazepam	30	50	5-65			53	0.45
	Placebo	30	50	20-60			57	
Duration of stay in hospital in days[b]	Diazepam	30	10	6-25	8	12		0.0008
	Placebo	30	8	6-13	7	8		
Improvement of finger floor distance at day 7 in cm[c]	Diazepam	27	-6.2[d]	12.7[e]	3	-12		0.65
	Placebo	28	-5.0[d]	14.9[e]	4	-10.5		

[a]Mann-Whitney U test for equivalence, [b]Mann-Whitney U test test for difference, [c]t-Test for difference, [d]Mean, [e]SD

Table 3: Clinical trial endpoint results

| Parameter[a]	Diazepam patients (%)	Placebo patients (%)	Risk ratio[b]	95% confidence interval	P value
Pain reduction of VAS of 50% or more	12/29 (41%)	23/29 (79%)	0.5	0.3-0.8	0.0015
Streight leg raise increase of 50% or more	7/29 (24%)	9/29 (31%)	1.1	0.6-1.8	0.79
Reduction of pain duration by 50% or more	15/29 (51%)	18/27 (66%)	0.8	0.5-1.2	0.26
Improvement of sensory loss	15/18 (83%)	19/22 (86%)	1.0	0.7-1.3	0.79
Reduction of paresis	6/27 (22%)	8/28 (28%)	0.8	0.3-2.0	0.59
Inability to work beyond day 28	16/29 (55%)	12/29 (41%)	1.3	0.7-2.2	0.43
Request for additional analgesics	15/29 (51%)	12/29 (41%)	1.3	0.7-2.3	0.36

[a]: N's were mostly 29 except for a few variables on which 1 or 2 subjects were missing data.

[b]: Risk or chance of the diazepam group relative to placebo

Table 4. Patient request for further analgesics in addition to diclofenac.

	Placebo (A, n=30)	Diazepam (B, n=30)
Ibuprofen	3	2
Paracetamol	1	3
Rofecoxib	0	3
Metamizol	8	8
Tramadol	7	6
Piritramid	2	0
Morphine	1	2
Tilidine	0	1
Amitryptiline	0	1

Figure 1. CONSORT flow chart
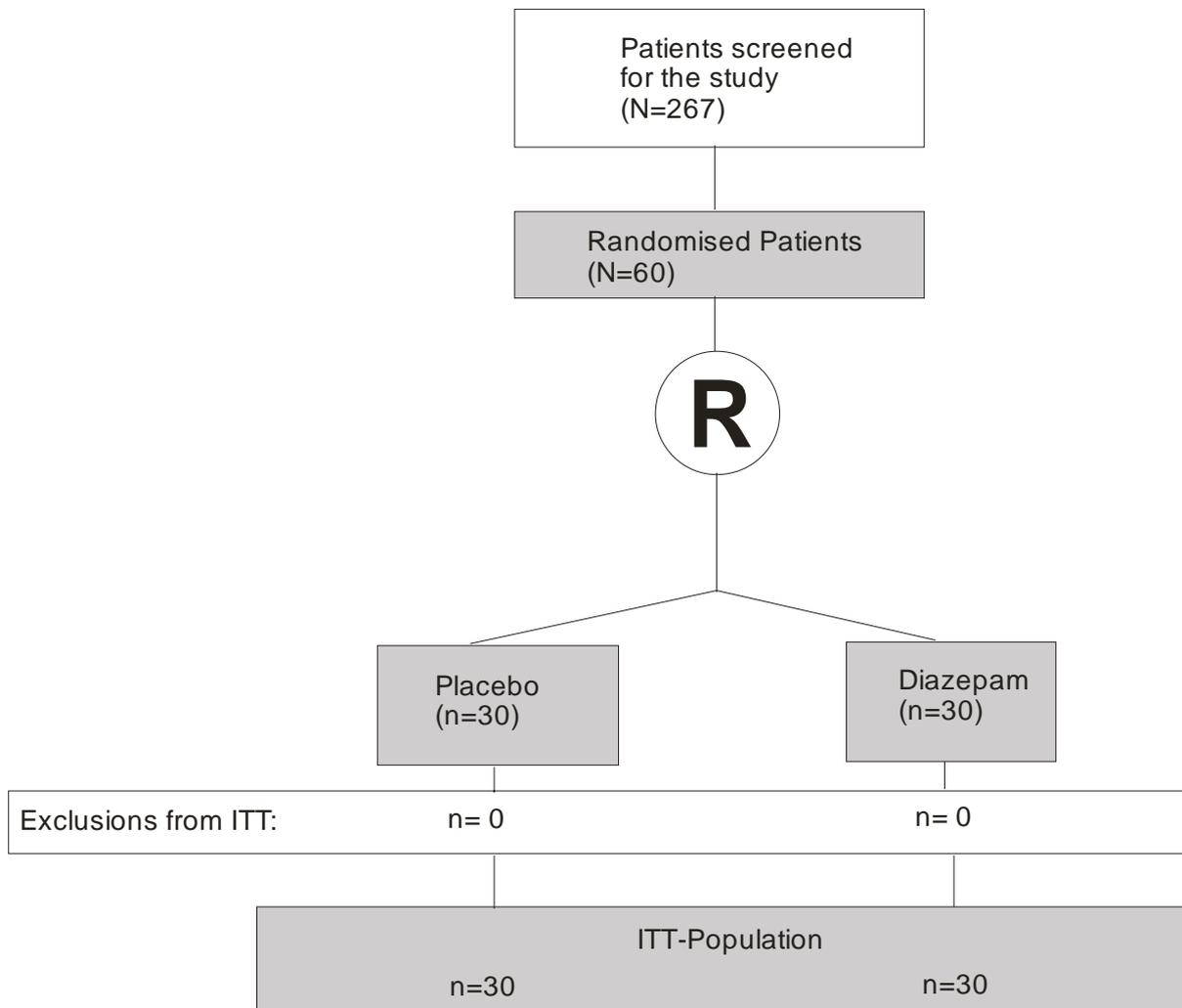
Supplementary Materials

Supplementary Table. Reasons for not including candidate patients in the trial.

Major reason	Patients (n)
Lumbar disc prolapse syndrome not confirmed clinically or on neuroimaging	107
No centralization of pain in first physiotherapy session	39
Prior surgical intervention at lumbar spine	14
Distance of referred pain on admission less than 10 cm	24
No informed consent for participation	13
Age beyond inclusion criteria	6
Benzodiazepine intake for more than 14 days	1
Language problems	3