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Randomized Trial

# Percutaneous Epidural Lysis of Adhesions in Chronic Lumbar Radicular Pain: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Background:** Chronic radicular pain can occur after disc pathology and failed back surgery. An evidence-based effective therapeutic option is not available nor does a gold standard exist.

**Objectives:** A randomized controlled trial to analyze the clinical efficacy of percutaneous epidural lysis of adhesions in chronic radicular pain.

**Study Design:** Prospective randomized placebo controlled interventional trial. Power calculation based on a feasibility trial.

**Setting:** Medical university centers.

**Methods:** Within 4 years a total of 381 patients with chronic radicular pain lasting longer than 4 months which failed to respond to conservative treatments were screened and 90 patients were enrolled. They were randomly assigned to receive either percutaneous neurolysis or placebo with concealed allocation in permuted blocks of 4 to 8, stratified by treatment center. The primary outcome measure was the differences in percent change of Oswestry Disability Index (ODI) scores 3 months after intervention. Secondary outcome measures were difference in percent change of ODI scores and Visual Analog Scale (VAS) 6 and 12 months after intervention and success rates defined as at least 50% reduction in ODI scores and VAS scores (mean change from baseline) at 3, 6, and 12 months after treatment. Explorative, 2-sided group comparisons for baseline characteristics between active treatment and controls were done using the t-test for 2 independent samples for quantitative data and Fisher's exact test for binary data.

**Results:** The ODI and VAS scores as well as the success rates for ODI vs VAS were significantly better 3, 6, and 12 months in the lysis group vs the control group. The ODI in the lysis group improved from 55.3 ± 11.6 to 26.4 ± 10.8 after 3 months. The placebo group improved from 55.4 ± 11.5 to 41.8 ± 14.6 ($P < 0.01$). VAS improved from 6.7 ± 1.1 to 2.9 ± 1.9 in the active group and from 6.7 ± 1.1 to 4.8 ± 2.2 ($P < 0.01$) after placebo. Twelve month follow-up shows further improvement, the differences remain significant. In multiple linear regression, forward and backward variable selection methods resulted in the same covariate model confirming the univariate result for group comparison in the primary analysis. No severe side effects occurred but minor transient neurological effects such as partial sensomotoric deficits did. One dura puncture and one catheter displacement were found.

**Limitations:** Specific effects of single treatment components cannot be specified because there was no imaging examination after treatment.

**Conclusion:** Based on the findings of our study as well as other studies, we believe the minimally invasive percutaneous adhesiolysis procedure should be the first choice treatment option for patients with chronic lumbosacral radicular pain who present with clinical history and findings similar to those of the patients enrolled in our study.

**Key words:** Lysis, low back pain, randomized controlled trial (RCT), placebo, epidural, radiculopathy, outcome, evidence-based medicine

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More than 20 years ago Racz and Holubec described a technique for lysis of epidural adhesions to treat lumbosacral radicular and/or low back pain (1-4). Since then, it has been used worldwide. The technique is minimally invasive and is relatively easy to perform following proper training compared to minimally invasive open techniques (2,5-11).

The fundamental premises on which the technique is based are that adhesions are present in the epidural cavity of patients with low back pain and/or radicular pain, the adhesions prevent epidurally injected medication from reaching intended targets, the adhesions contribute to the pathogenesis of pain by immobilizing nerve roots, and pain relief can be obtained by removing barriers that prevent drugs from reaching the target site and prevent the free movement of nerve roots (12-14). Chronic lumbar radicular pain is defined as a clinical syndrome of back and leg pain which could be accompanied by neurological deficits such as sensory, reflex, or motor deficits in a nerve root distribution lasting more than 12 weeks (15). Lumbar radicular pain is reported to have a lifetime prevalence of 5.3% in men and 3.7% in women (16). Lumbar radicular pain due to a disc protrusion resolves spontaneously in 23 – 48% of patients, but up to 30% will still have significant symptoms after one year. Up to 20% will be out of work, and 5 - 15% will undergo surgery (17,18). The effect of epidural cortisone was first described in 1953 (19). Mechanical compression of nerve roots induce lumbar radicular pain which also can be triggered by different proinflammatory chemical agents (12,20-22). Mechanical and chemical effects cause ectopic neuron firing (23). Epidural steroids around the affected nerve root are known to inhibit this inflammatory process (23-27). The positive short-term effect of epidural cortisone is described by several authors but the long-term effects still have conflicting evidence (28,29). One year after epidural steroid injection, improvement of pain and disability has been reported for 36% to 43% of patients (25,30,31).

In addition to local anesthetic and corticosteroid, hypertonic saline (10% NaCl) and hyaluronidase are used for the lysis technique for better opening of interconnected spaces. Too, hypertonic saline is noted to have some local anesthetic action (32,33) and C-fiber selectivity (34). Studies have shown lower rates of pain recovery and higher success rates (3,6,13).

In brief, the technique involves performing an epidurogram to identify filling defects indicative of epidural scarring, advancing a catheter in the anterolateral epidural space into the adhesions, injecting hyaluronidase to facilitate adhesiolysis and normal saline to hydraulically separate adhesions and wash out epidural proinflammatory cytokines, and injecting anti-inflammatory and analgesic drugs and hypertonic saline to treat pain, inflammation, and edema. Since the technique was introduced, various investigators have used modifications of it, but the basic approach has remained unchanged.

Many studies have been done to evaluate the safety and efficacy of the procedure (4,7,11,35,36). The studies, as well as extensive clinical experience, attest to the efficacy, as well as, the safety of using epidural neurolysis to treat radicular and low back pain. Nevertheless, there is still demand for more evidence, especially from studies meeting high standards of evidence-based medicine. The purpose of the study reported here was to compare placebo vs. epidural neurolysis for treating lumbosacral radicular pain using a cohort, random group assignment, prospective double-blinded study with one year follow-up.

## Methods

The study was conducted in 4 orthopedic universities specializing in interventional pain management. The objective of this prospective, randomized, double-blind study was to compare the response of patients with lumbosacral radicular pain to lysis of epidural adhesions as described by Racz et al vs. placebo intervention (3,8,37).

Ninety of the 381 patients screened during the enrollment phase were included in the study. All 90 patients were randomly assigned to receive either percutaneous neurolysis or placebo with concealed allocation in permuted blocks of 4 to 8, stratified by treatment center (n = 4), with the use of a computer-generated random list (Fig 1). Concealment of randomization was guaranteed by non-transparent envelopes. Both patients and assessing physicians were blinded to the assigned group. In designing the study, we adhered to the standardized guidelines of good clinical practice (GCP) from the International Conference on Harmonization ICH (38,39). The study was based on Consolidated Standards of Reporting Trials (CONSORT) guidelines (40).

The study protocol was submitted and approved by the Ethics Committee of the Technical University of Munich. The variable chosen for determination of group size was the Oswestry Disability Index (ODI) (0 – 100%

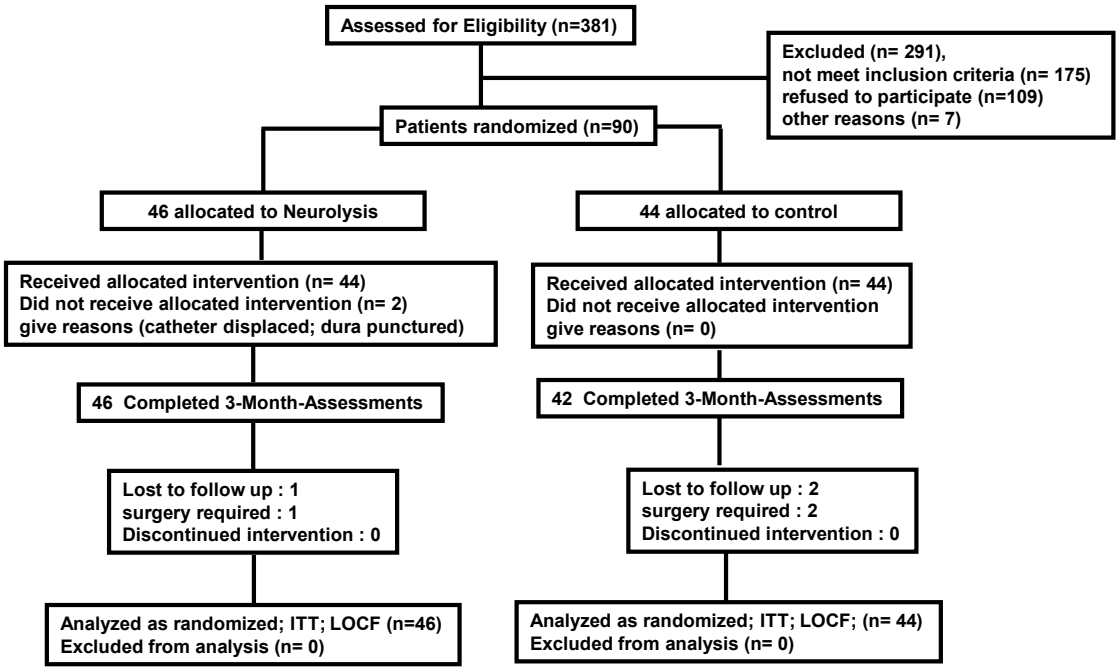


Fig. 1. *Flow chart of a the randomized controlled trial in accordance to the CONSORT Statement.*

disability; minimal disability [= 0%] to either bed-bound or exaggerating symptoms [ = 100%]) (41). To calculate precise study power and to establish the study design, a feasibility trial was performed. In 2001 and 2002 a total of 61 patients who fit the defined inclusion criteria received percutaneous lysis of adhesions using the same technique, medication, primary criteria, and follow-up intervals (5,37). As a second step, the final study protocol was adjusted and finally designed. Based on data taken from the feasibility trial, it was determined that a sample size of 37 in each group will have 80% power to detect a difference in means of 0.2 (i.e. 20% difference of relative ODS change between the 2 groups) assuming that the common standard deviation in the primary outcome is 0.3 (i.e., 30%) using a 2 group t-test with a 0.05 2-sided significance level. With 10% dropout, we end up with 90 patients. A similar sample size calculation is given in Gerdesmeyer et al (5). Inclusion criteria (Table 1) included lumbosacral radicular pain of at least 4 months duration, positive Laségue test, results of clinical examination confirming presence of lumbosacral radicular pain, and presence of CT/MRI pathology. Patients were excluded from the study if their blood coagulation parameters were abnormal or if they had absolute spinal stenosis, motor deficiencies, tumors involving the spine, diabetes mellitus, or a history of allergy to medications used for the study. Patients were hospitalized and underwent a 3-day treatment regimen.

The lysis procedure was performed using a caudal approach. After a 16 gauge RK needle was placed onto the sacral canal via the sacral hiatus under fluoroscopic guidance, 10 mL of radiopaque contrast material (Solutrast 300 [Iopamidol], ALTANA Pharma AG Byk-Gulden-Straße 2, 78467 Konstanz, Germany) was injected to confirm epidural placement and identify any filling defects suggestive of epidural adhesions. Next a Tun-L-Kath® (Epimed International, 141 Sal Landrio Dr Johnstown, NY 12095, USA) was inserted through the epidural needle and advanced to the antero-lateral area of the filling defect. Then local anesthetic (10 mL 0.25% bupivacaine) was injected through the catheter followed by 10 mL of preservative-free saline containing 150 U/mL of hyaluronidase. Saline (10 mL, 10%)

Table 1. *Inclusion and exclusion criteria.*

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Chronic lumbar radicular pain without neurologic motor deficits after disc protrusion or after failed disc surgery<br>• Age > 18 years<br>• Ability to give written informed consent after being told of the potential benefits and risks of participating in the study<br>• Signed patient informed consent paper<br>• 4 months of unsuccessful conservative treatment i.e., must have undergone at least 1 unsuccessful non-pharmacological treatment and at least 2 unsuccessful pharmacological treatments<br>• Time gap of at least:<br>• 6 weeks since the last corticosteroid injection<br>• 4 weeks since the last anesthetic injection; iontophoresis, ultrasound and electromyostimulation<br>• 1 week since the last NSAIDs<br>• 2 days since the last prescription or non-prescription analgesics, heat, ice, massage, stretching<br>• Score of > 4 on the VAS scale<br>• Score of > 45 on Oswestry Score<br>• Time interval of > 1 week after last pain medication except rescue medication of of 14g Paracetamol max/week or 14g Metamizol/week<br>• Time interval of 6 weeks after epidural injections | • Patients with chronic lumbar radicular pain with neurologic motor deficits after disc protrusion or after failed disc surgery<br>• Rheumatoide disease, Collagenosis, Diabetes mellitus,<br>• Cancer<br>• Inflammation (acut, subacut, chronic) with significant pathologic laboratory findings<br>• Vertebral body fracture<br>• Immunsupressive therapy<br>• Long time cortisone therapy<br>• Clinical relevant heart and lung disease<br>• Disturbance of coagulation<br>• Spinal stenosis<br>• Polysegmental disc disease<br>• Previous epidural catheter interventions<br>• Hypersensitivity to local anesthesics, Hyaluronidase, contrast<br>• Liver disorders<br>• Poor physical conditions<br>• Pregnancy<br>• Periphere nerve entrapement<br>• Workers compensation<br>• Urogentital or sexual disfunction |

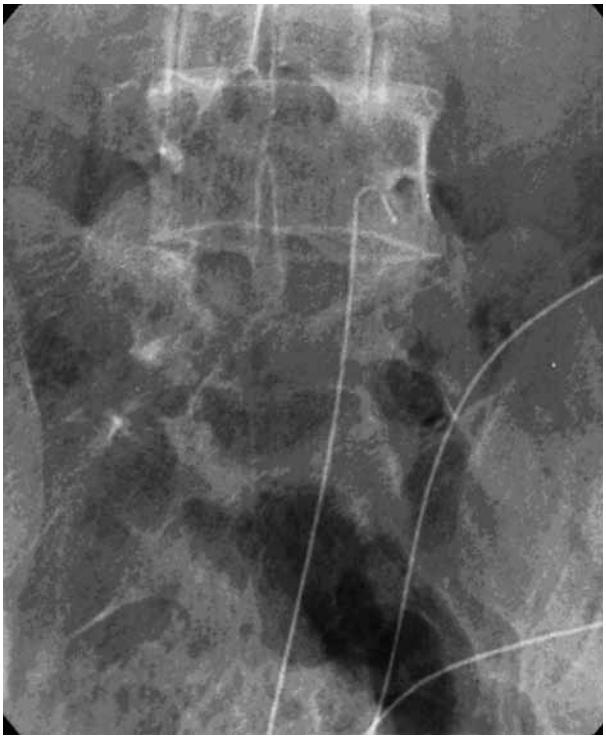

Fig. 2. *Antero – postero view: Placement of the tip of the catheter into the ventro-lateral epidural space to L4/5.*

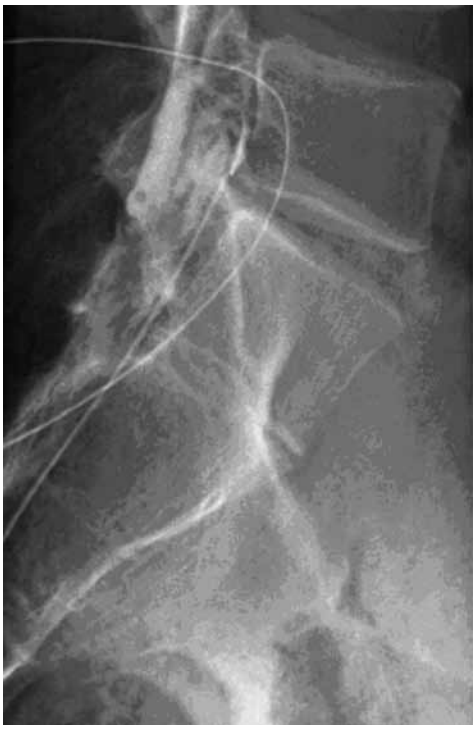

Fig. 3. *Lateral view: Placement of the tip of the catheter into the ventro-lateral epidural space and epidurogram to L4/5.*

containing 40 mg triamcinolone was then injected slowly along with 2 mL of 0.25% bupivacaine. Figures 2 and 3 show the correct positioning of the tip of the catheter into the ventro-lateral position of L4/5. The catheter was left in place.

On each of the next 2 days, 10 mL of 0.25% bu-

pivacaine was injected through the catheter, followed by slow injection of 10 mL 10% saline and 2 mL 0.25% bupivacaine. Then the catheter was removed.

In the placebo group, a needle and catheter were inserted as for the lysis group except the needle was intentionally inserted so it did not enter the spinal canal and the catheter was inserted into the subcutaneous tissue overlying the afflicted level. Each patient received through the catheter 10 mL of preservative-free saline. On each of the next 2 days, 10 mL of preservative-free saline was injected, then the catheter was removed. Following the 3 injection series, all subjects were prescribed physical therapy with no activity restrictions. Patients were provided rescue medication of 14g paracetamol maximum/week (not to exceed 2 g/day) or 14g metamizol maximum/week if requested.

The primary outcome measure was the differences in percent change of ODI scores 3 months after intervention. Secondary outcome measures were difference in percent change of ODI scores 6 and 12 months after intervention plus the differences in percent change of Visual Analog Scale (VAS) scores (0 = no pain, 10 cm = worst possible pain) and success rates defined as at least 50% reduction in ODI scores and VAS scores (30% difference in outcome [mean change from baseline]) at 3, 6, and 12 months after treatment.

Patients, outcome assessors, and care providers were blinded during the study period; they were all unaware of the randomization and intervention given by the pain physician. The orthopaedic surgeon giving the repetitive injections was also unaware of the allocated treatment. The injection products were concealed from the patients.

## Statistical Analysis

Baseline characteristics are given as mean ± standard deviation for quantitative variables and absolute or relative frequencies for qualitative variables. Explorative, 2-sided group comparisons for baseline characteristics between active treatment and controls were done using the t-test for 2 independent samples for quantitative data and Fisher's exact test for binary data.

The primary analysis is the comparison between the 2 treatment groups with respect to the primary outcome based on the intention-to-treat (ITT) population. As a sensitivity analysis for the primary outcome, missing values were replaced by "last observation carried forward" (LOCF). Additional analyses for the primary outcome are based on the per protocol population. Medians for primary and secondary outcomes were compared between the 2 groups using the Mann-Whitney U-test; 95% confidence intervals for median group differences are shown in brackets. Clinically relevant success rates in the 2 groups were compared using Fisher's exact test. *P*-values are 2-sided and subject to a significance level of 0.05. Results for the univariate primary analysis were confirmed in multiple linear regression with percent change in ODI as dependent and group, gender, and BMI as independent variables. Forward and backward variable selections were used to account for possible multicollinearity in the covariate model. In addition, possible heterogeneity between the centers was accounted for using the random effects model of Dersimonian and Laird (42). The following software packages were used for statistical analyses: CIA (Confidence interval analysis), Version 2.1.2, StatsDirect Version 2.5.7, and SPSS Version 16.0.2.

## Results

Of the 90 patients meeting eligibility criteria to participate in this study, 46 were randomly assigned to receive neurolysis and 44 were assigned to the placebo group (Fig. 1). Statistical analysis revealed no group difference between epidemiological data and ODI or VAS scores at baseline (Table 2). Two subjects in the treatment group did not receive the assigned therapy

*Table 2. Demographic data at baseline.*

| Subject Demographics | | | |
|---|---|---|---|
| | **Placebo** | **Treated** | ***P*-value** |
| No Pts | 44 | 46 | |
| Male (%) | 41 | 59 | 0.14 |
| Age (years) | 47 ± 13 | 49 ± 13 | 0.58 |
| BMI | 25.9 ± 3.2 | 25.4 ± 3.4 | 0.44 |
| Duration of radicular pain (months) | 7.1 ± 2.8 | 6.7 ± 2.6 | 0.57 |
| ODI | 55.4 ± 11.5 | 55.3 ± 11.6 | 0.97 |
| VAS | 6.7 ± 1.1 | 6.7 ± 1.1 | 0.82 |

either because the dura was punctured or the catheter became displaced. One subject in the treatment group and 2 subjects in the placebo group required surgery and were lost to follow-up.

The ODI and VAS scores as well as the success rates for ODI vs VAS were significantly better 3, 6, and 12 months in the lysis group vs the control group (Table 3, Fig. 4A,B). The trend was for all measures in both groups

Table 3. *Follow-up data 3, 6, and 12 months after intervention.*

| Outcome of primary criteria 3 months after intervention | | | |
|---|---|---|---|
| | **Placebo group** | **Lysis group** | ***P*-value** |
| ODI | 41.8 ± 14.6 | 26.4 ± 10.8 | <0.01 ** |
| VAS | 4.8 ± 2.2 | 2.9 ± 1.9 | <0.01 ** |
| >50% improvement ODI | 7/42 | 26/45 | <0.01 ** |
| >50% improvement VAS | 12/42 | 31/45 | <0.01 ** |
| **Outcome of primary criteria 6 months after intervention** | | | |
| ODI | 37.3 ± 13.1 | 11.9 ± 8.7 | <0.01 ** |
| VAS | 3.8 ± 1.6 | 1.4 ± 0.9 | <0.01 ** |
| >50% improvement ODI | 4/37 | 31/42 | <0.01 ** |
| >50% improvement VAS | 14/36 | 32/42 | =0.01 ** |
| **Outcome of primary criteria 12 months after intervention** | | | |
| ODI | 30.7 ± 14.2 | 9.6 ± 9.3 | <0.01 ** |
| VAS | 2.8 ± 1.5 | 1.2 ± 1.0 | <0.01 ** |
| >50% improvement ODI | 9/26 | 28/31 | <0.01 ** |
| >50% improvement VAS | 18/26 | 29/31 | <0.032 ** |

** indicate significance $P < 0.05$)

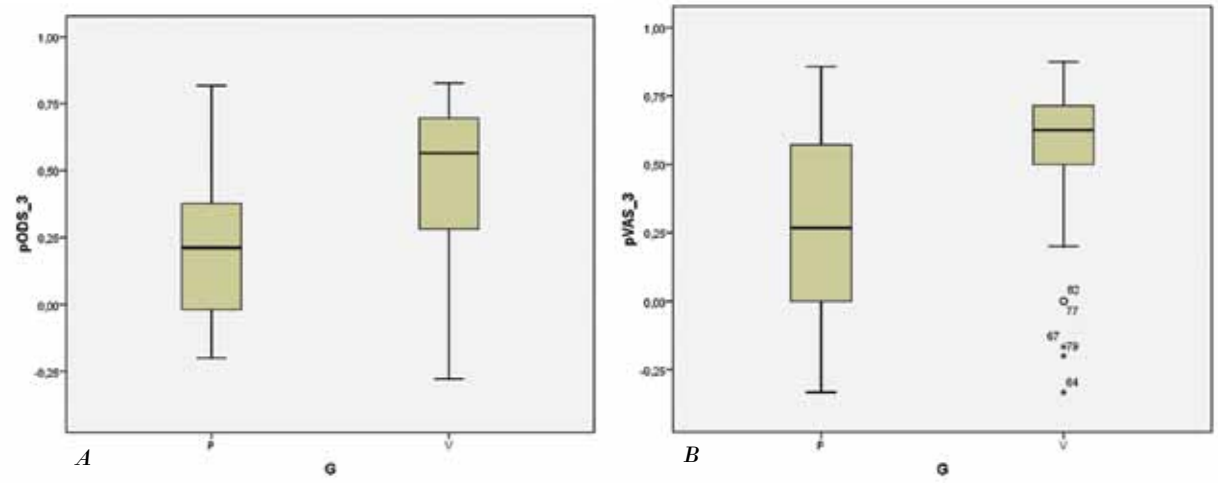


Fig. 4. ***A** Percent change of Oswestry Disabiliy Score of the lysis and placebo group 3 month after intervention compared to baseline. The primary outcome variable is shown as the relative difference in Oswestry Disability Score (ODS) between baseline and month 3 relative to the baseline, expressed as percent change. *Significantly different $P < 0.001$. **B**: Percent change of VAS scale of the active and placebo group 3 month after intervention compared to baseline. The primary outcome variable is the relative difference in VAS Score (VAS) between baseline and month 3 relative to the baseline, expressed as percent change. *Significantly different $P < 0.001$.*

to show improvement during the 12 month follow-up. Interestingly, the success rate based on 50% or more improvement of ODI and VAS shown in the lysis group was generally consistent. There was some disparity in success rates in the placebo group with more success based on VAS vs ODI. The improvement in pain and disability for subjects in the placebo group at 3 months was of a magnitude consistent with a placebo response.

Heterogeneity between the centers did not affect significance for the primary analysis (Fig. 5A,B). In multiple linear regression, forward and backward variable selection methods resulted in the same covariate model confirming the univariate result for group comparison in the primary analysis. Additional analyses with LOCF for missing values and a per protocol analysis resulted also in *P*-values < 10-3 supporting the initial primary analysis.

Considering possible heterogeneity between the centers using a random effects model did not affect the explorative results of secondary analyses with any of these *P*-values < 0.002 for group comparisons.

Not unexpectedly, some subjects in each group reported procedure-related pain during the intervention. In the lysis group a total of 34 subjects reported pain compared to 20 patients receiving identical placebo treatment. In the active group 3 patients reported swelling as did 2 in the control group. Clinically no objective sign of any swelling was found and these findings were interpreted as a kind of paraesthesia. Transient neurologic deficits occurred more frequently in the lysis group immediately after intervention which was expected as a treatment-related side effect (42 vs 6). All neurological deficiencies (numbness, paralysis, or motor weakness) resolved spontaneously within the hospitalization period. No adverse event or any side effect was found at 3, 6, or 12 months follow-up.

Technical difficulties, dura puncture of the catheter into spinal canal (Fig. 6) and shearing of the outside

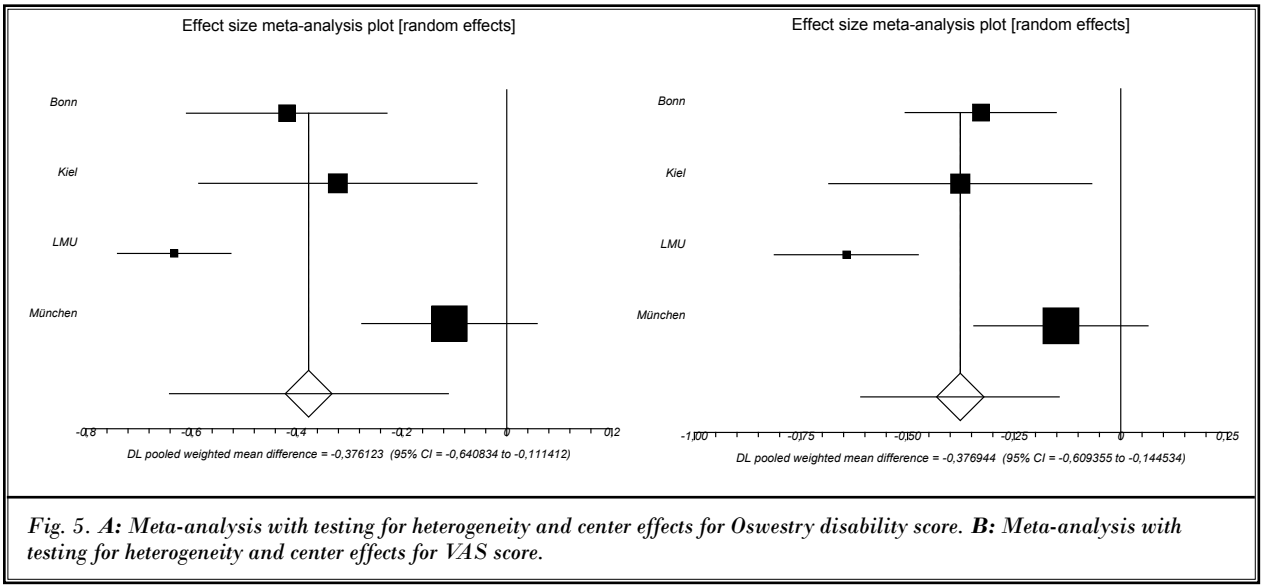


*Fig. 5. **A:** Meta-analysis with testing for heterogeneity and center effects for Oswestry disability score. **B:** Meta-analysis with testing for heterogeneity and center effects for VAS score.*

Fig. 6. *Shearing of the outside coating of the catheter.*

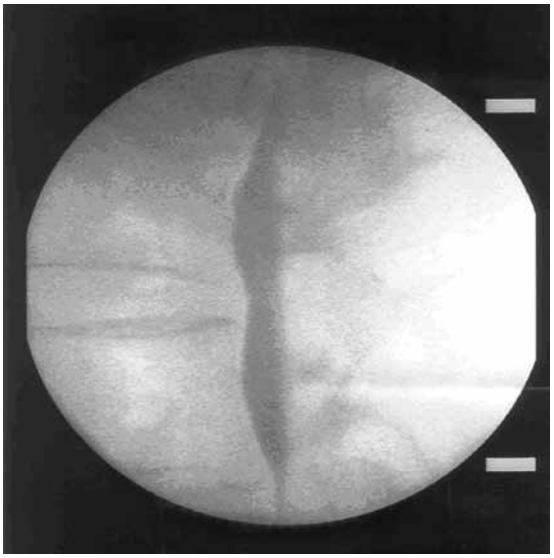

Fig. 7. *Catheter displacement into the spinal canal with myelogram.*

catheter coating (Fig. 7), were observed once in each group. In the case of dura puncture into the spinal canal, the catheter was removed and readvanced until correct position and epidurogram was shown. In case of shearing the outside catheter coating, resistance by maneuvering the catheter was perceived by the surgeon and the complete system was removed and the procedure started from the beginning with a new catheter system and introducer needle.

## Discussion

Epidural steroid injections have been used for 5 decades to treat lumbar radicular pain (43). Causes of chronic radicular pain include mechanical compression of nerve roots as well as different proinflammatory substances (20,22,44), which trigger ectopic neuron firing (23). Pain reduction, mechanical decompression around the compressed nerve root, and inhibitation of these inflammatory mediators are induced by injecting steroids into the epidural space or around the affected nerve. Until now there has been conflicting evidence for the potential benefit of these epidural steroid injections (28,29,45-47).

Results of studies of epidural steroid treatment differ. Some studies show a moderate short-term benefit in contrast to others which show little difference between epidural steroid and placebo injections (25,27,29-31,48,49).

Results of this prospective, double-blind, randomized, placebo-controlled study clearly show that patients with chronic lumbosacral radicular pain after disc protrusion or after failed back surgery have significantly less pain and disability for at least one year following percutaneous epidural adhesiolysis than patients do receiving placebo. There were no unexpected complications. All complications were short lasting. Technical difficulties such as catheter displacement outside the epidural space and partial catheter shearing of the Teflon-like outside coating were observed once in each group (Figs. 6 and 7).

The findings of this study complement positive findings of other studies that examined the safety and efficacy of epidural adhesiolysis (2,5-8,11,13,37,50). It is also concluded from systematic reviews that there is fair evidence that percutaneous adhesiolysis is also effective in relieving low back and/or leg pain caused by post lumbar surgery syndrome and spinal stenosis (2,7,10,13). Furthermore, they found that the incidence of complications from adhesiolysis is low and generally minimal and self-limited (5,7,11,32,34,51,52). Other authors concluded, based on an earlier systematic review (2009), that there is strong evidence for the use of adhesiolysis for post lumbar laminectomy syndrome (35).

The literature search done by Helm et al (7) found 1,474 articles potentially relating to the key questions concerning whether percutaneous adhesiolysis is effective for the treatment of intractable low back and/or leg pain due to either post lumbar surgery syndrome or spinal stenosis. Of these, 15 were considered for inclusion in their systematic review; 6 were randomized, controlled trials and 9 were observational studies. Only 5 randomized, controlled trials and 3 observational studies met criteria for inclusion. We believe the study we report here meets or exceeds the criteria Helm et al applied to selecting investigations for their final review. It is a high quality study providing data that strongly supports the use of epidural adhesiolysis for treating chronic lumbar radicular pain after disc protrusion or after failed back surgery.

Important to consider is that treatment options for the patients who qualified for enrollment in this study are very limited. Requirements included 4 months of unsuccessful conservative therapy including at least one unsuccessful non-pharmacological treatment and at least 2 unsuccessful pharmacological treatments (Table 1).

Noteworthy is that only one published article reported negative results with epidural adhesiolysis (53). A basic flaw of the study was failure of the investigators

to place the catheter at the target site – pathology in the anteriolateral epidural space. Among other issues, this oversight emphasizes that proper training and experience is required before one can conduct trials of adhesiolysis (5,8,37).

According to Helm et al (7), the major issue related to the conduct of research pertaining to adhesiolysis revolves around the control group or placebo (5,7). They commented that placebo control neural blockade is not realistic. In the present study we addressed this by using the same approach for both the control group and the lysis group, except the catheter in the control group was deliberately misplaced outside of the spinal canal and saline only was injected through the catheter. Patients in both groups were prescribed rescue medication and physical therapy. Both treatments had failed prior to the patients entering the study, but inclusion was judged to be essential for humane reasons and for standardization. It is interesting that it appears there has been a large placebo effect in the control group. In a previous study, Veihelmann et al (11) found no significant placebo effect in a control group treated with physiotherapy. Apparently, placement of the catheter and saline injection in our study produced the placebo effect. This placebo effect is related to significant interventions such as surgery and interventional options like percutaneous lysis or epiduroscopy (54,55).

Most randomized placebo controlled trials with excellent blinding techniques are known to have a great placebo effect size which can be enhanced by interventions (54,56). If some surgical interventions were performed, the placebo effect size is even greater (55,57,58).

For interventional pain procedures the enhanced placebo effect is estimated but not determined in size until now. The data of our randomized trial show the effect size of a placebo intervention by placing the catheter system into the subcutaneous layer as well as the effect after percutaneous lysis of adhesions. The mean change of the VAS improved from 6.7 ± 1.1 to 2.9 ± 1.9 in the active group 3 months after neurolysis. Within the same period the placebo group showed a reduction from 6.7 ± 1.1 to 4.8 ± 2.2 on the VAS scale. Similar findings occur on the Oswestry disability score. The mean ODI score of the control group improved from 55.4 ± 11.5 to 41.8 ± 14.9 at month 3 after intervention compared to the active group with an improvement from 55.3 ± 11.6 to 26.4 ± 10.8 at 3 months after intervention. This tendency continued up to one year after intervention. Further improvement was found in both groups. The enhanced placebo effect in the control group improved slightly. VAS decreased to 2.8 after 12 months compared to 6.7 at baseline. The Oswestry Score improved continuously to 30.7. It appears to be a long-lasting enhanced placebo effect. These findings need to be confirmed in another trial.

In a recent multicenter, blinded, randomized controlled trial in outpatient multidisciplinary back clinics in Norway, 133 patients with chronic radicular pain were enrolled. They all had pain lasting longer than 12 weeks and were randomly assigned to get subcutaneous sham injections of 2 mL 0.9% saline, caudal epidural injections of 30 mL 0.9% saline, or caudal epidural injections of 40 mg triamcinolone acetonide in 29 mL 0.9% saline. All patients received 2 injections within a 2 week interval. The change in the Oswestry Disability questionaire was designed as the primary criteria which was comparable to our trial. At 52 week follow-up, 27% patients still had a lumbar radicular pain, with no significant differences seen between the groups. At the same time 50% of the patients stated that they had received "much" or "some" benefit from the treatment, with no significant differences seen in favor for any group ($P$ = 0.81) (59). In contrast to the results after caudal cortisone injections, the ODI and VAS scores, as well as, the success rates for ODI vs VAS were significantly better 3, 6, and 12 months in the lysis group compared to the control group. The trend was evident for all measures in both groups showing improvement at 12 month follow-up. Also the success rate based on > 50% improvement of ODI and VAS shown in the lysis group was generally consistent. The improvement in pain and disability for subjects in the placebo group at 3 months was of a magnitude consistent with a placebo response. The study from Iversen et al (59) and our trial cannot be compared but it is obvious that the effect size after placebo treatment shows a similar tendency. In our lysis trial 18 out of 26 patients had more than 50% improvement after placebo intervention which is better than it was for the Iversen trial. But the main difference could be demonstrated in the active group. Ninety percent of the patients were found to have > 50% improvement on the Oswestry disability questionnaire and more than 93% have > 50% improvement on the VAS. The similarity of the outcome after placebo could be used to estimate similar placebo efficacy in both trials but the difference in outcome after lysis intervention is much better. This study has now

confirmed initial findings by earlier investigations of the lysis procedure (5,6,8,11,50).

The working mechanism is discussed as a combined effect of local lavage of proinflammation cytokines, reduction of swelling, lysis of adhesions, desensitization and modification of neuromodulation, and local anesthesia. The mechanical effect is debatable. Birkenmaier et al (60) have shown that the catheter itself is not able to have significant mechanical effects in an experimental study setup. An experimental laboratory setup was used to analyze the main forces that can be exerted by manipulating a catheter in the epidural space or by injecting fluids through a catheter: axial forces, torsional forces, and hydraulic effects. The maximum axial forces measured under extremely tight catheter guidance were 7 newton (N), whereas the maximum forces under estimated clinical conditions were between one and 2 N. The maximum torsional forces measured were 0.3 N. The maximum flow that could be achieved using normal saline and the maximum possible thumb pressure was 0.48 mL/s. The authors themselves discussed the obvious limitations that the experimental setup did not represent the real clinical and anatomic environment (57).

Evidence exists that "compartments" may be present in the epidural space, and when fluid is injected it sequentially fills these compartments as the pressure in each compartment exceeds the pressure needed to break tissue barriers to intercompartmental flow in order to allow spread of fluid into the adjoining compartment (61).

The presence or absence of epidural adhesions is difficult to demonstrate by conventionally used studies such as standard x-ray or computerized axial tomography (CAT) scans. The epidurography technique described by several authors before seems appropriate to visualize epidural adhesions by filling defects. These filling defects by epidurography are minimized in size after successfully performed epidural lysis of adhesions. The epidural space is opened up by injecting a high volume epidural if the catheter is placed directly into the zone of adhesions (3,5,8,62).

The role of hyaluronidase has been questioned (63). Only one randomized trial was published. In this trial Heavner et al (6) were able to demonstrate that hyaluronidase has a positive impact on outcome. Hyaluronidase is used to start biological lysis of the tight cell junctions between different anatomic sheets. Epidurographic examinations by injecting contrast medium before and after the lysis procedure show the differences of the contrast spread and the reopening of adhesions. The combined application of hyaluronidase, the large volume of fluid, and the low direct mechanical effects which are recently confirmed in an experimental study, leads to the local dissection of the anatomic structures into the region of adhesions which exist in chronic local inflamed anatomic regions as the epidural space if extruded disc material or bulged discs are present. The lysis effect is limited to adhesions between these anatomic sheets. If postsurgical scars were present, a lysis of these tight structures is impossible and the lysis procedure as tested is not indicated (60). The published data indicated that the forces needed to rupture scars 4 – 10 week after surgery are within a range of 60 to 90 N which is far beyond the possibilities of the lysis technique (64). Manchikanti et al (8,50) have shown differences in outcome by modifying the original lysis protocol as published previously. The application of cortisone and hypertonic saline combined with the lysis of adhesions has a better outcome compared to local epidural injection of anesthetics and cortisone alone. The best results were found if the full treatment cycle was performed (8).

One limitation of our study is the unknown effect of each single treatment component. Based on our findings we cannot give any recommendation if the full cycle of treatment and parameters used in the percutaneous lysis of adhesions is necessary to achieve these results or if one of the options such as hyaluronidase, hypertonic saline, dosage of cortisone, and mechanical catheter effect or just the volume injected has possibly no significant effect on outcome. Further studies have to focus on these specific effects of each single parameter. The other limiting aspect is the missed imaging examination by MRI after intervention. The authors cannot give any statement if adhesions re-occur or how much lysis of adhesions correlates with clinical effects. The last aspect is the effect of placebo intervention as performed in our trial, an unspecific intervention with a specific clinical response. Surprisingly the effect reaches clinically relevant size and has shown further improvement up to 12 month after intervention. It cannot be ruled out that the subcutaneous catheter placement far outside the epidural space has a therapeutic effect.

## Conclusions

Based on the findings of our study, we strongly believe the minimally invasive percutaneous lysis of adhesions should be the first choice treatment option for patients with chronic lumbosacral radicular pain who present with clinical history and findings similar to those of the patients enrolled in our study.

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