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# Intradiscal glucocorticoids injection in chronic low back pain with active discopathy: a randomized controlled study

Short Title: Intradiscal glucorticoid for active discopathy

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## Abstract

**Background**. The benefit of an intradiscal injection of corticosteroids for low back pain with active discopathy is not totally resolved.

**Objective.** The objective of this study was to estimate the clinical efficacy of an intradiscal injection of glucocorticoids versus lidocaine in patients with low back pain and active discopathy (Modic 1 changes).

**Methods**. A prospective, single-blind, randomized controlled study was conducted in 2 tertiary care centers with spine units. We enrolled 50 patients (mean age 50 years; 46% women) with lumbar active discopathy on MRI and failure of medical treatment for more than 6 weeks. Participants were randomly assigned to receive an intradiscal injection of glucocorticoids (50 mg prednisolone acetate [GC group], n=24) or lidocaine (40 mg [L group], n=26) by senior radiologists. Outcome measures were low back pain in the previous 8 days (10-point visual analog scale), Dallas Pain Questionnaire, Oswestry Disability Index, analgesic treatment and work status at 1, 3 and 6 months as well as pain at 1, 2 and 3 weeks. The primary outcome was change in pain between baseline and 1 month.

**Results**. Data for 39 patients (78%; 17 in the GC group, 22 in the L group) were analyzed for the primary outcome. Pain intensity was significantly reduced at 1 month in the GC versus L group (mean [SD] -2.7 [2.3] and +0.1 [2.0], $p<0.001$) but not at 3 and 6 months. At 1 and 3 months, the groups significantly differed in daily activities of the Dallas Pain Questionnaire in

favour of the GC group. The groups did not differ in consumption of analgesics or professional condition at any time. No serious intervention-related adverse events occurred. Study limitations included patients lost to the study because of injection-related technical issues in the L5/S1 disc and short time of follow-up.

**Conclusion**. As compared with intradiscal injection of lidocaine, intradiscal injection of prednisolone acetate for low back pain with active discopathy may reduce pain intensity at 1 month but not at 3 and 6 months.

**Registration:** ClinicalTrials.gov: NCT01694134

**Key Words:** low back pain, intradiscal injection, randomized control trial

## Introduction

Chronic low back pain (LBP) is a major burden to society and to the individuals affected. It is the leading cause of years lived with disability (1). Research into disc degeneration is expanding and has questioned the clinical importance of many spine imaging findings and clinical symptoms of LBP. In 1980, Modic et al. (2) described changes in vertebral endplate bone marrow on MRI. Modic type 1 change is associated with LBP (odds ratio 4.0, 95% CI 1.1-14.6) and is considered a strong predictor of pain (3). Indeed, this endplate signal change is rarely observed in asymptomatic patients (5% to 20%) (4,5). Patients with Modic 1 changes have an inflammatory pain rhythm and poor chronic LBP outcome (6). The origin of this local inflammation is unknown and predisposing factors are probably multifactorial (chemical and mechanical) (7).

In patients with Modic 1 changes, therapeutic studies are scarce and consensus is lacking on the right therapy (8). Fayad et al. showed in a retrospective study that 54% of patients with Modic 1 changes had more than 50% improvement at 1 month after an intradiscal injection of acetate prednisolone (9). Cao et al. showed in a double-blind randomized controlled study that visual analog scale (VAS) score for pain and Oswestry Disability Index improved significantly at 3 or 6 months after glucocorticoids injection but not after saline injection in the control group (10). However, this study has been criticized by several authors (11,12), questioning its reproducibility; in particular, the respective outcomes were unusual, with a particularly high effect in the treatment group and no effect in the control group even in the short term, despite the healing process.

Recently, Nguyen et al. showed in a prospective randomized controlled study that intradiscal glucocorticoids injection reduced LBP intensity at 1 month but not at 12 months as compared with discography alone (13). At 1 month, the mean reduction in LBP intensity from baseline was better in the glucocorticoids than control group (32.5 vs 17.5). Paradoxically, at 3 months, pain scores were higher in the glucocorticoids than discography alone group (13).

These results still question the interest of intradiscal glucocorticoids treatment for onset time and duration of the effect in active discopathy and the impact of control intervention. Our study aimed to evaluate at 1, 3 and 6 months the benefit of an intradiscal injection of glucocorticoids in individuals with LBP and Modic 1 changes as compared with intradiscal injection of lidocaine.

## Materials and method

### Study design and population

This was a prospective, single-blind, randomized controlled study: patients and evaluators were blinded; only the physician giving injections was aware of the treatment. Patients were

recruited in the Physical Medicine and Rehabilitation and Rheumatology departments of Montpellier and Nîmes university hospitals, France, from July 2012 to August 2016. The present study is reported according to the CONSORT checklist (Supplementary Fig. S1).

Patients aged 18 to 80 years, with LBP for more than 6 weeks, failure of conservative treatment, and Modic 1 endplate changes were eligible. The exclusion criteria were previous low back surgery, contra-indication to infiltration and discopathy with Modic 1 signal changes on multiple lumbar levels.

After being informed about the study, patients giving their written informed consent were included in the trial and randomized to one of the 2 study groups by using a computer-generated list of random numbers with a 1:1 ratio. Randomization was centralized (performed by the clinical research unit of Montpellier university hospital with Ennov clinical V6 software), stratified on center and with variable block sizes. This centralized randomization procedure using electronic case-report forms ensured allocation concealment. The study protocol was approved by the university ethics committee and was registered at ClinicalTrials.gov (NCT01694134).

## Interventions

Included patients were randomized to receive prednisolone acetate (gluticosteroids [GC group]) for the intervention group or lidocaine (L group) for the control group. The injections were given by senior radiologists with more than 10 years' experience (CC, YT for Montpellier center and LA, VP for Nîmes center). To standardize this procedure and to ensure equal quality of treatment application, participating physicians were trained in performing the intradiscal injection procedure under fluoroscopic guidance according to a protocol. The first step of the procedure was identical in the 2 study groups and consisted of an intradiscal injection with 0.5 ml contrast dye (Iohexol-Omnipaque 300) that allowed for performing

discography to confirm the position of the needle within the nucleus. The second step of the procedure involved injection of 2 ml prednisolone acetate (hydrocortancyl, 2.5%, Sanofi-Aventis France) in the experimental group and 2 ml lidocaine (lidocaine hydrochloride, 2%, 20 mg/mL, Aguettant) in the control group. The radiologists were not blinded because the color of the product differed between groups. Radiologists were not allowed to communicate with patients and other physicians about treatment. After the treatment, the patient had bed rest for at least 2 hr with observation in the daycare surgery unit.

On the basis of data available at the time of the study, lidocaine was used in the control group for several reasons: first, no treatment has demonstrated any effect for this condition; second, an analgesic effect was expected for patients with pain undergoing an infiltration procedure; third, immediate effects of anesthetic treatment should better contrast the effect at 1 month and later; finally although anesthetic solutions are not currently used for active discopathy, this should produce pain relief in the lumbar disc.

Patients were followed up for 6 months with clinical consultations at 1 month (± 4 days), 3 months (± 7 days) and 6 months (± 14 days) after injection.

## Outcomes

LBP intensity in the previous 8 days was assessed by the patient by using a visual analog scale (VAS), with scores ranging from 0 (no pain) to 10 (maximum pain). The primary outcome was the change in pain score between baseline and 1 month.

Secondary outcomes were assessed during clinical visits and/or were self-reported by patients in diaries between visits. LBP intensity (VAS) was measured at 1, 2, and 3 weeks and at 3 and 6 months after injection. Disability was assessed with the Oswestry Disability Index, ranging from 0 to 100. The impact (in percentage) of LBP for daily activities, work and leisure activities, anxiety/depression and social interest was assessed by the Dallas Pain

Questionnaire (14). For each subscale, the higher the score, the higher the impact of pain. Finally, quality of life was assessed by the Medical Outcomes Study Short-form 36 (SF-36) (15), with scores ranging from 0 (poorest quality of life) to 100 (best possible quality of life). All outcomes except the pain score were measured at 1, 3 and 6 months. All questionnaires were validated in French: Oswestry Disability Index (17) Dallas Pain Questionnaire (16), SF-36 (17).

Analgesics consumption was collected in the patient's diary and at each visit. Professional status and safety outcomes were collected at each visit. All adverse events (AEs) were collected and reported.

The initial declaration on ClinicalTrials.gov was completed after the first inclusion and needed updates to correct some discrepancies with the protocol approved by the ethics committee: first, the primary outcome was wrongly declared at 6 months, whereas the sample size and prespecified statistical analysis were planned at 1 month. Second, the employment status was not initially specified in ClinicalTrials.gov but was planned in the protocol and recorded during the trial; it certainly is interesting for clinicians and has been reported at ClinicalTrials.gov and in the paper.

## Statistical considerations

*Sample size:* From data from a similar study involving intradiscal lumbar corticosteroid infiltration (9), the clinically relevant minimal difference in the variation (J1-J30) of the VAS score for pain between the 2 groups was established at 2 cm (standard deviation 2 cm). The number of participants was estimated at 18 per group with alpha 5% and power 80% under a bilateral hypothesis. Given an expected rate of lost to follow-up of 10%, we estimated that we needed 40 participants. This estimate had to be increased during the study (substantial modification: favourable opinion of the CPP on October 7, 2015) because of an unanticipated

difficulty in performing disc injections in L5-S1 for 5 patients due to the inability to reach the disc. Therefore, the total number of participants was increased by 25% and therefore 25 per group.

### Statistical analysis

The primary analysis was performed according to the intention-to-treat principle and involved all patients who were randomly assigned and for whom data for the primary outcome at baseline and 1 month were available (full analysis set). After checking that missing data were missing at random, multiple imputation (18) was implemented to confirm our result (sensitivity analysis).

Baseline characteristics are reported with mean (SD) (or median and interquartile range [IQR]) for continuous variables and frequencies (%) for categorical variables. Comparisons of primary outcome and other continuous variables involved Student *t* test (if normally distributed) or Wilcoxon rank test otherwise. Two-sided $P<0.05$ was considered statistically significant. The effect size was estimated by Cohen's *d*. Values of *d* range from 0.01 to 2 and can be interpreted, as suggested by Sawilowsky (19), with the thresholds 0.01/0.20/0.50/0.80/1.20/2 as very small/small/medium/large/very large/huge, respectively. Statistical analyses were performed with SAS v9.4 (SAS Institute, Cary, NC, USA).

## Results

### Study participants

We randomly assigned 50 participants to receive glucocorticoids or lidocaine injection (Fig. 1). For 5 patients, the intervention was not performed because it was not technically possible owing to a loss of height of the intervertebral disc; 3 participants withdrew during follow-up for medical reasons (hepatitis E, lung cancer, diffuse pain) and 3 participants had missing data

for the primary outcome. Thus, data for 39 patients (17 in GC group and 22 in L group) were analyzed for the primary outcome.

Intradiscal injection was performed in L4-L5 for 21 participants, in L5-S1 for 22, in L2-L3 for 5, and in L3-L4 for 2. The injections were done on the day of randomization at a median (IQR) of 51 (81) days after the MRI. Baseline characteristics of participants are in Table 1.

## Pain assessment

The 2 groups significantly differed in the primary outcome: at 1 month, mean (SD) pain score decreased by 2.7 (2.3) VAS points in the GC group and increased by 0.1 (2.0) points in the L group ($p<0.001$) (Fig. 2). Effect size was very large, with a Cohen's *d* of 1.36. After multiple imputation of missing data (for 9 patients), mean pain score evolution was -2.1 (95% confidence interval -3.1 ; -1.12) for the GC group and -0.1 (-1.18 ; 0.8) for the L group. Variation in mean pain scores differed significantly between groups as soon as the second week and up to 1 month, but the difference was no longer significant at 3 and 6 months (Fig. 2). Evolution of mean VAS scores revealed significantly lower pain scores in the GC than L group from week 1 to month 1 but no differences at 3 and 6 months (Supplementary Fig. S2).

At 1 month, the proportion of patients with night awakenings was significantly lower in the GC than L group (36.6% vs 81%, $p=0.004$). Morning stiffness duration and LBP mobility was better but not significantly in the GC than L group.

## Disability and quality of life

Variation in mean Dallas Pain Questionnaire subscores is displayed in Figure 3. The mean (SD) "daily activities" subscore improved significantly more in the GC than L group at 1 month (-21.2 [21.9] vs -3.3 [11.8], Cohen's *d* 0.94) and 3 months (-30.6 [21.5] vs -9.4 [15.1],

Cohen's *d* 1.14), and the "anxiety and depression" subscore improved significantly more in the GC than L group at 3 months (-18.6 [22.1] vs 0.3 [22.7], Cohen's *d* 0.85). Variation in the "work and leisure activities" and the "social interest" subscores did not differ between groups during follow-up. Likewise, the variation in Oswestry score did not differ between groups at 1 month (Supplementary Fig. S3). The groups did not differ in physical and mental component summary scores of the SF-36 during follow-up (Supplementary Fig. S4).

### Work status (Table 2)

For 33 patients with available data at follow-up, 4 (12%) showed a change in professional status over 6 months: 2 participants in the GC group and 1 participant in the L group returned to work but were on sick leave at baseline, and 1 participant in the GC group who was professionally active at baseline was retired at 3 months. All other participants had the same professional status during follow-up.

### Adverse effects

Serious AEs related to LBP were reported in both groups and concerned hospitalization for usual care of chronic LBP (3 in the GC group and 4 in the L group).

## Discussion

Our study demonstrates that an intradiscal injection of glucocorticoids can reduce pain in individuals with LBP and active discopathy from the first week to 1 month as compared with an intradiscal injection of lidocaine. Pain reduction at 1 month from baseline was -2.7/10 points, which is comparable to that found by Nguyen et al. (-32.5/100) (13). The reduction in pain intensity increased gradually from 1 week to 1 month (Fig. 2, Supplementary Fig. S2) and demonstrates for the first time quick pain relief for people with LBP. Although the daily

activities subscore of the Dallas Pain Questionnaire was improved significantly at 1 and 3 months, our results confirm the persistent discomfort because the other subscores did not change, which probably explains the lack of gain in quality of life. Those results are consistent with previous data (13).

The pain relief resulting from the intradiscal glucocorticoids injection is maximal between 15 days and 1 month. After this, the effect weakly worsened until 3 months and did not change at 6 months. This rebound of pain between 1 and 3 months after intradiscal glucocorticoids agrees with Nguyen et al. (13). The anti-inflammatory effect seems to be reproducible in the short term but may be cleared by psychosocial confounding factors later. One or 2 ml of hydrocortancyl seems to produce similar effects.

In contrast, we found no clinical benefit in the lidocaine group, as was recently described (20). First, lidocaine cannot be reasonably considered a placebo, which is confirmed by the absence of effects at 1 month. Second, the relative negative effect questions the safety of lidocaine in the disc as was previously described (21). Third, the pain relief observed at 3 and 6 months confirms the participation of the healing process (11) as for discography alone (13). Therefore, lidocaine does not seem to be a therapeutic option for active discopathy nor an appropriate comparator.

Apart from technical concerns, we did not evidence side effects in the GC group, which confirms the safety of soluble glucocorticoids for intradiscal injection. The hypothesis that disc infection could explain part of active discopathy still remains controversial (22). No antibiotic prophylaxis was proposed in the present study and no discitis was reported during follow-up. In agreement with most previous studies of intradiscal injection of GCs (9,13,23,24), the low-grade infection hypothesis seems unlikely.

NICE 2016 guidelines do not recommend intradiscal injections for chronic LBP (25). The place of intradiscal injection of glucocorticoids for LBP remains to be defined, in

249 particular regarding other types of low back injections (26). Epidural glucocorticoids injection
250 is commonly used for radicular pain with scarce scientific evidence (23). Facet injection
251 seems to be less effective in active discopathy (27). Finally, only exercises demonstrate a
252 better improvement for patients with Modic 1 changes versus other MRI abnormalities (28).
253 Therefore, the place of intradiscal injection to maintain physical activity can be questioned.

254 Our study has several limitations. We included 50 individuals, but only 39 could be
255 analyzed, mainly because the injection was not possible for technical reasons. The injection in
256 L5/S1 disc was not possible when the height of the intervertebral disc was too small and when
257 the slope of the last segment made access to the needle difficult. Patients who had missing
258 data because they were not injected and those who withdrew due to unrelated medical reasons
259 were fairly well distributed between the 2 groups. In addition, 3 patients in the GC group had
260 missing data for the primary outcome. After multiple imputation, the mean difference in pain
261 evolution at 1 month was 2 (vs 2.8 in the complete-case analysis). Moreover, confidence
262 intervals of pain evolution in each group show that this evolution was still significantly
263 different between groups after multiple imputation. Thus, the impact of missing data on the
264 effect size and significance of the observed difference seems small, despite a slight
265 overestimation. In the same way, the poor, indeed negative, effect of lidocaine may explain
266 part of this effect size, which is unusual in this treatment. Moreover, the follow-up was
267 probably too short to detect side effects but was adapted to detect an effect. Considering
268 clinical manifestations of discitis, an endpoint at 1 year seems preferable. Because no MRI
269 was scheduled at the end of the trial, we cannot guarantee the lack of consequences after disc
270 injection (destructive disc disease, calcification, discitis). Finally, the difference between the
271 groups in SF-36 subscores at baseline may have limited impact on the results because the
272 analysis was performed from score differences.

LBP is the main cause of disability worldwide; however, gaps between evidence and practice remain (29,30). The identification of a specific cause of LBP, as in Modic changes, should not let us forget the biopsychosocial approach recommended for chronic LBP. Indeed, the individuals have experienced pain for several months or years and there are multiple contributors to pain and disability. Recent guidelines did not recommend injection for LBP management, only for severe radicular pain (31). Results of the present study highlight the pain relief induced by intradiscal injection of glucocorticoids for individuals with LBP whose nociceptive pain can be related to active discopathy.

## Conclusion

As compared with an intradiscal injection of lidocaine, an intradiscal injection of glucocorticoids may reduce pain intensity in individuals with LBP and active discopathy (Modic 1 changes) from the first week after injection to 1 month. This clinical effect was not maintained at 3 and 6 months and may be explained in part by a specific effect of the active comparator.

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Figure Captions

**Figure 1.** Flow of participants in the study.

**Figure 2.** Variation in low back pain (visual analog scale [VAS]) intensity. Data are mean (SD). Visual analog scale (VAS) scores at weeks 1, 2 and 3 were self-reported by patients in diaries, whereas VAS scores at 1, 3 and 6 months were completed during follow-up visits.

**Figure 3.** Variation in Dallas subscores during follow-up.

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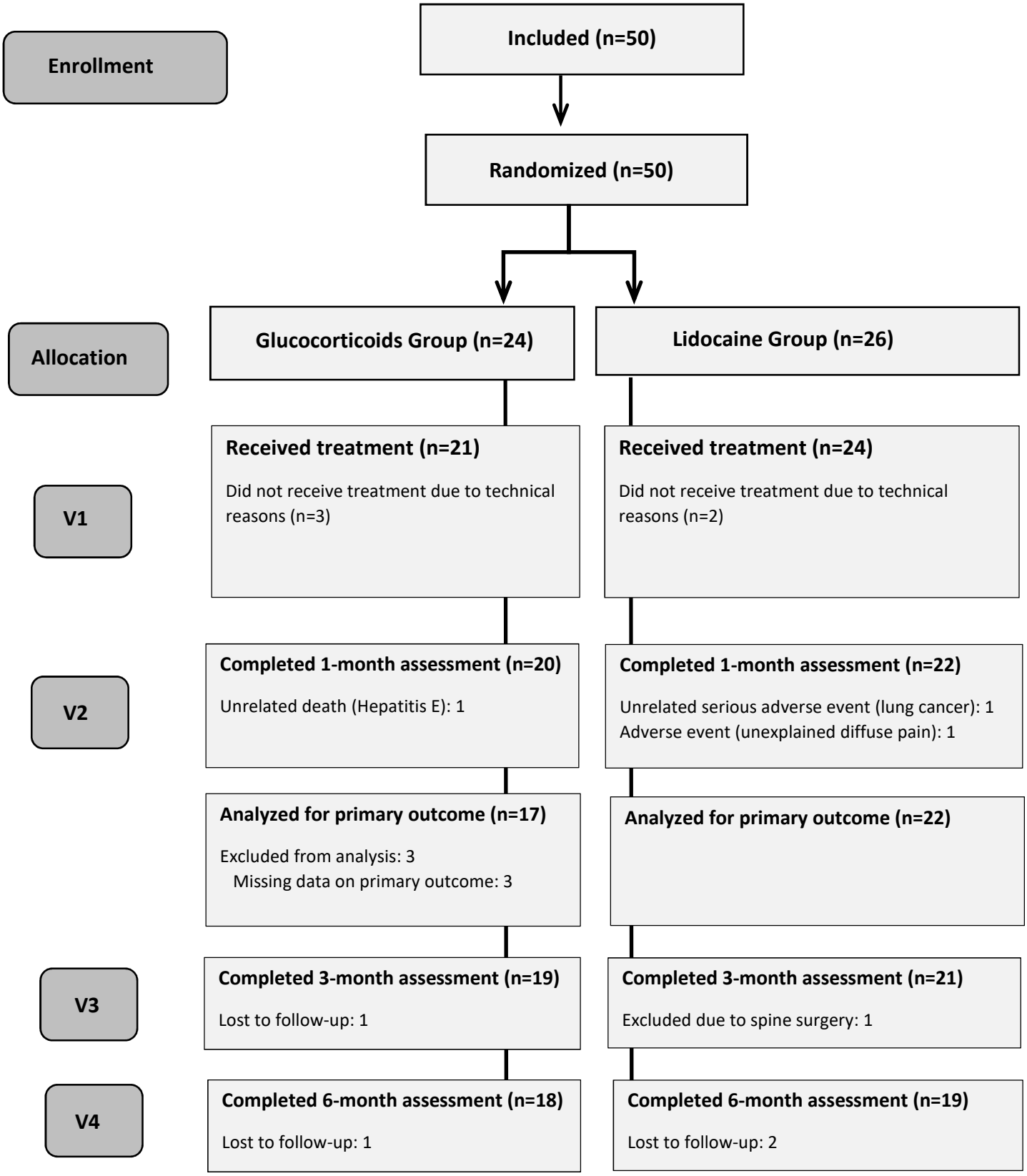
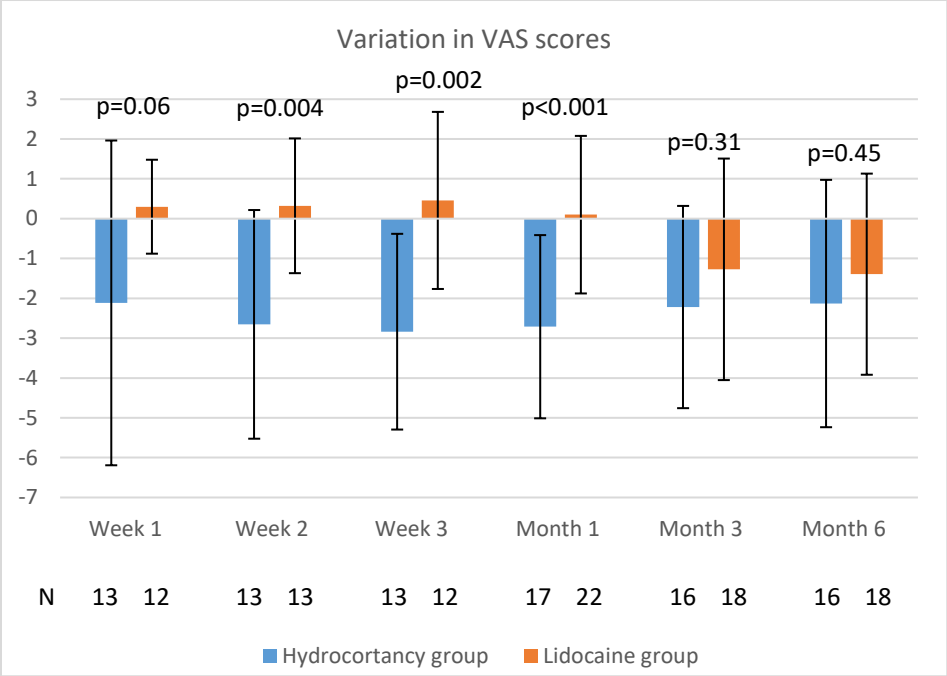
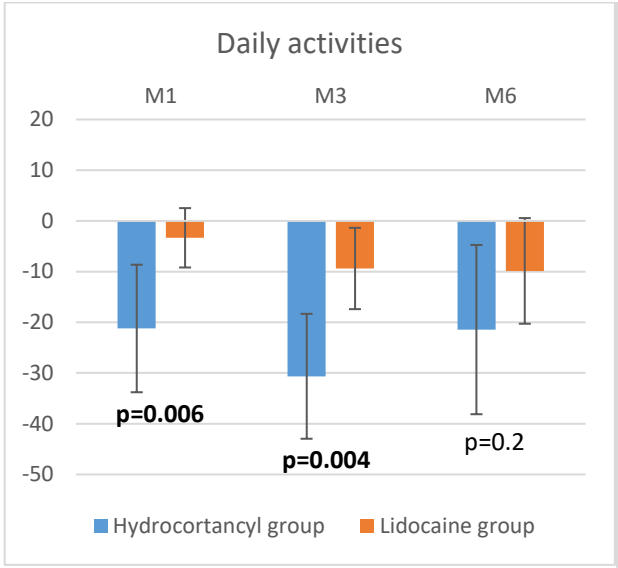
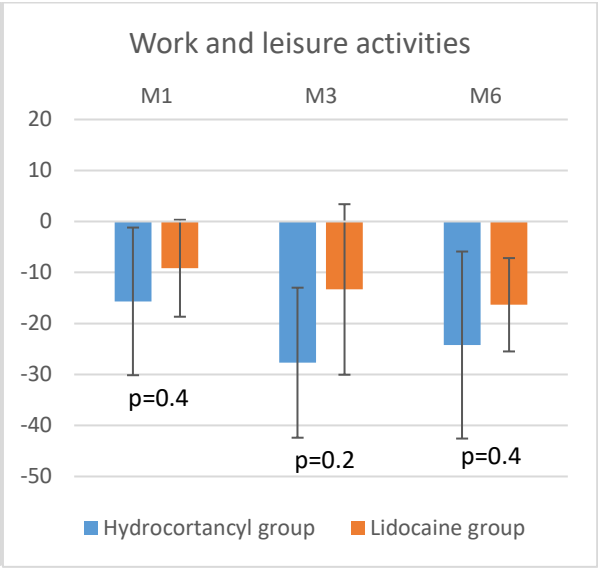
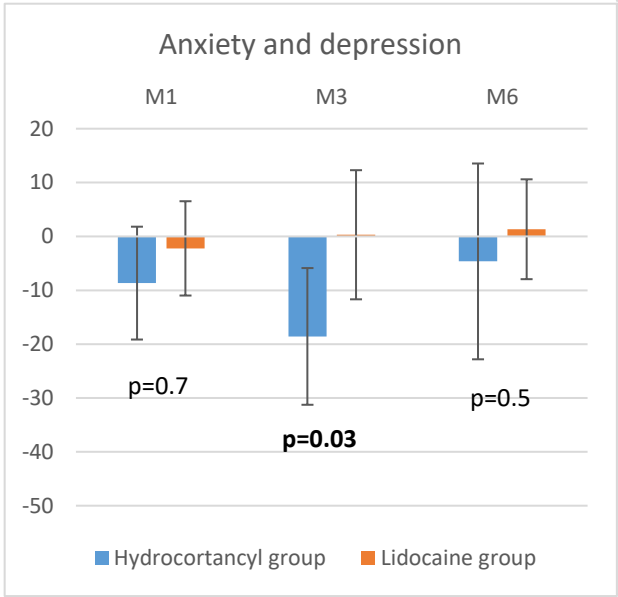

Enrollment
Included (n=50)
Randomized (n=50)
Allocation
Glucocorticoids Group (n=24)
Lidocaine Group (n=26)
V1
Received treatment (n=21)
Did not receive treatment due to technical reasons (n=3)
Received treatment (n=24)
Did not receive treatment due to technical reasons (n=2)
V2
Completed 1-month assessment (n=20)
Unrelated death (Hepatitis E): 1
Completed 1-month assessment (n=22)
Unrelated serious adverse event (lung cancer): 1
Adverse event (unexplained diffuse pain): 1
Analyzed for primary outcome (n=17)
Excluded from analysis: 3
Missing data on primary outcome: 3
Analyzed for primary outcome (n=22)
V3
Completed 3-month assessment (n=19)
Lost to follow-up: 1
Completed 3-month assessment (n=21)
Excluded due to spine surgery: 1
V4
Completed 6-month assessment (n=18)
Lost to follow-up: 1
Completed 6-month assessment (n=19)
Lost to follow-up: 2


Variation in VAS scores
p=0.06
p=0.004
p=0.002
p<0.001
p=0.31
p=0.45
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
Week 1
Week 2
Week 3
Month 1
Month 3
Month 6
N 13 12 13 13 13 12 17 22 16 18 16 18
Hydrocortancy group
Lidocaine group


Daily activities
M1
M3
M6
20
10
0
-10
-20
-30
-40
-50
p=0.006
p=0.004
p=0.2
Hydrocortancyl group
Lidocaine group


Work and leisure activities
M1
M3
M6
20
10
0
-10
-20
-30
-40
-50
p=0.4
p=0.2
p=0.4
Hydrocortancyl group
Lidocaine group


Anxiety and depression
M1
M3
M6
20
10
0
-10
-20
-30
-40
-50
p=0.7
p=0.03
p=0.5
Hydrocortancyl group
Lidocaine group

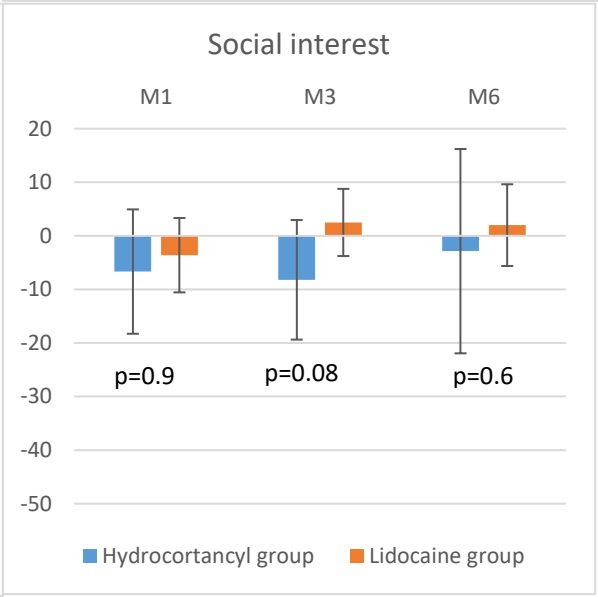

Social interest
M1
M3
M6
20
10
0
-10
-20
-30
-40
-50
p=0.9
p=0.08
p=0.6
Hydrocortancyl group
Lidocaine group

**Table 1.** Baseline characteristics of the population.

| | N | Glucocorticoids group | N | Lidocaine group |
|---|---|---|---|---|
| Sex, female, no. (%) | 24 | 9 (38) | 26 | 14 (54) |
| Age (year) (SD) | 24 | 50 (14) | 26 | 50 (8.7) |
| **Employment status,** no. (%) | **24** | | **26** | |
| **Professionally active** | | **11 (46)** | | **9 (35)** |
| **On sick leave** | | **6 (25)** | | **8 (31)** |
| **Retired** | | **7 (30)** | | **5 (19)** |
| **Disabled, unemployed** | | **0** | | **4 (15)** |
| Night awakening, no. (%) | 24 | 16 (67) | 26 | 20 (77) |
| Morning stiffness duration (min) | 24 | 30 [15-60] | 25 | 45 [15-60] |
| **Drugs use,** no. (%) | | | | |
| **Analgesics** | **22** | **12 (55)** | **26** | **13 (50)** |
| **NSAIDs** | **22** | **6 (27)** | **26** | **6 (23)** |
| BMI, kg/m$^2$, mean (SD) | 19 | 24.9 (3.9) | 20 | 23.7 (4) |
| Schober test score (mm), mean (SD) | 24 | 28 (11.8) | 25 | 29 (14) |
| Finger-to-floor test score (cm) | 24 | 21 [13.5-31] | 24 | 11 [2.5-29.5] |
| **VAS for the past 8 days,** mean (SD) | **22** | **6.4 (1.8)** | **26** | **6.4 (1.9)** |
| | | **6.0 [5.5-8.0]** | | **6.4 [5.5-8.0]** |
| **Dallas,** mean (SD) | | | | |
| **Daily activities** | **20** | **72 (10)** | **23** | **68 (14)** |
| **Work and leisure activities** | **19** | **70 (14)** | **23** | **64 (22)** |
| **Anxiety depression** | **20** | **44 (23)** | **23** | **33 (23)** |
| **Social interest** | **20** | **36 (23)** | **23** | **30 (22)** |
| **SF-36 scores**, mean (SD) | | | | |
| **PCS score** | **20** | **35.9 (5.3)** | **23** | **31.1 (7.7)** |
| **MCS score** | **20** | **33.4 (12.3)** | **23** | **40.3 (12)** |
| **Oswestry** | **19** | **40 (11)** | **19** | **41 (15)** |
| Disease duration (years) | 21 | 1.8 [0.6-8.1] | 25 | 2 [0.8-12.2] |
| Injection site, no. (%) | 24 | | 26 | |
| L2-L3 | | 4 (17) | | 1 (4) |
| L3-L4 | | 0 | | 2 (8) |
| L4-L5 | | 9 (37) | | 12 (46) |
| L5-S1 | | 11 (46) | | 11 (42) |

NSAIDs, non-steroidal anti-inflammatory drugs; VAS, visual analog scale; SF-36, Medical Outcomes Study Short-form 36; PCS, physical component summary; MCS, mental component summary

Data are median [interquartile range] unless indicated. Data in bold are part of the outcomes specified in the protocol; other data are from the clinical folder (not prespecified in the protocol).

**Table 2.** Clinical and work status outcomes at 1 month after the injection.

| | | Glucocorticoids group | | Lidocaine group | p |
|---|---|---|---|---|---|
| Employment status, n (%) | 20 | | 22 | | NA |
| Professionally active | | 9 (45) | | 7 (32) | |
| On sick leave | | 5 (25) | | 8 (36) | |
| Retired | | 6 (30) | | 4 (18) | |
| Disabled or unemployed | | 0 | | 3 (14) | |
| Night awakening, n (%) | 19 | 7 (36.6) | 21 | 17 (81.0) | 0.004 |
| Morning stiffness duration (minutes) | 20 | 17.5 [1-52.5] | 20 | 30 [10-60] | 0.236 |
| Schober test score (mm), mean (SD) | 20 | 30.9 (11.0) | 21 | 40.5 (26.5) | 0.132 |
| **Drug use,** n (%) | **20** | | **21** | | |
| **Antalgics** | | **12 (60)** | | **12 (57)** | **0.85** |
| **NSAIDs** | | **3 (15)** | | **4 (19)** | **1.0** |

NA, not applicable

Data are median [interquartile range] unless indicated.

Data in bold are part of the specific criteria of the protocol; other data are from the clinical folder (not prespecified in the protocol).