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

Short Title: Intradiscal glucocorticoid for active discopathy

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1 **Intradiscal glucocorticoids injection in chronic low back pain with active discopathy: a**
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3

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5

6

7 **Abstract**

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

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

13 **Methods.** A prospective, single-blind, randomized controlled study was conducted in 2
14 tertiary care centers with spine units. We enrolled 50 patients (mean age 50 years; 46%
15 women) with lumbar active discopathy on MRI and failure of medical treatment for more than
16 6 weeks. Participants were randomly assigned to receive an intradiscal injection of
17 glucocorticoids (50 mg prednisolone acetate [GC group], n=24) or lidocaine (40 mg [L
18 group], n=26) by senior radiologists. Outcome measures were low back pain in the previous 8
19 days (10-point visual analog scale), Dallas Pain Questionnaire, Oswestry Disability Index,
20 analgesic treatment and work status at 1, 3 and 6 months as well as pain at 1, 2 and 3 weeks.
21 The primary outcome was change in pain between baseline and 1 month.

22 **Results.** Data for 39 patients (78%; 17 in the GC group, 22 in the L group) were analyzed for
23 the primary outcome. Pain intensity was significantly reduced at 1 month in the GC versus L
24 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
25 months, the groups significantly differed in daily activities of the Dallas Pain Questionnaire in

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

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

33

34 **Registration:** ClinicalTrials.gov: NCT01694134

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

36

37

38 **Introduction**

39 Chronic low back pain (LBP) is a major burden to society and to the individuals affected. It is
40 the leading cause of years lived with disability (1). Research into disc degeneration is
41 expanding and has questioned the clinical importance of many spine imaging findings and
42 clinical symptoms of LBP. In 1980, Modic et al. (2) described changes in vertebral endplate
43 bone marrow on MRI. Modic type 1 change is associated with LBP (odds ratio 4.0, 95% CI
44 1.1-14.6) and is considered a strong predictor of pain (3). Indeed, this endplate signal change
45 is rarely observed in asymptomatic patients (5% to 20%) (4,5). Patients with Modic 1 changes
46 have an inflammatory pain rhythm and poor chronic LBP outcome (6). The origin of this local
47 inflammation is unknown and predisposing factors are probably multifactorial (chemical and
48 mechanical) (7).

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

59 Recently, Nguyen et al. showed in a prospective randomized controlled study that
60 intradiscal glucocorticoids injection reduced LBP intensity at 1 month but not at 12 months as
61 compared with discography alone (13). At 1 month, the mean reduction in LBP intensity from
62 baseline was better in the glucocorticoids than control group (32.5 vs 17.5). Paradoxically, at
63 3 months, pain scores were higher in the glucocorticoids than discography alone group (13).

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

69

70 **Materials and method**

71 **Study design and population**

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

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

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

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

89

90 Interventions

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

99 discography to confirm the position of the needle within the nucleus. The second step of the
100 procedure involved injection of 2 ml prednisolone acetate (hydrocortancyl, 2.5%, Sanofi-
101 Aventis France) in the experimental group and 2 ml lidocaine (lidocaine hydrochloride, 2%,
102 20 mg/mL, Aguettant) in the control group. The radiologists were not blinded because the
103 color of the product differed between groups. Radiologists were not allowed to communicate
104 with patients and other physicians about treatment. After the treatment, the patient had bed
105 rest for at least 2 hr with observation in the daycare surgery unit.

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

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

114

115 Outcomes

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

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

124 Questionnaire (14). For each subscale, the higher the score, the higher the impact of pain.
125 Finally, quality of life was assessed by the Medical Outcomes Study Short-form 36 (SF-36)
126 (15), with scores ranging from 0 (poorest quality of life) to 100 (best possible quality of life).
127 All outcomes except the pain score were measured at 1, 3 and 6 months. All questionnaires
128 were validated in French: Oswestry Disability Index (17) Dallas Pain Questionnaire (16), SF-
129 36 (17).

130 Analgesics consumption was collected in the patient's diary and at each visit.

131 Professional status and safety outcomes were collected at each visit. All adverse events (AEs)
132 were collected and reported.

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

140

141 Statistical considerations

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

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

152

153 Statistical analysis

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

159 Baseline characteristics are reported with mean (SD) (or median and interquartile
160 range [IQR]) for continuous variables and frequencies (%) for categorical variables.
161 Comparisons of primary outcome and other continuous variables involved Student *t* test (if
162 normally distributed) or Wilcoxon rank test otherwise. Two-sided $P < 0.05$ was considered
163 statistically significant. The effect size was estimated by Cohen's *d*. Values of *d* range from
164 0.01 to 2 and can be interpreted, as suggested by Sawilowsky (19), with the thresholds
165 0.01/0.20/0.50/0.80/1.20/2 as very small/small/medium/large/very large/huge, respectively.
166 Statistical analyses were performed with SAS v9.4 (SAS Institute, Cary, NC, USA).

167

168 **Results**

169 Study participants

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

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

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

180

181 Pain assessment

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

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

194

195 Disability and quality of life

196 Variation in mean Dallas Pain Questionnaire subscores is displayed in Figure 3. The mean
197 (SD) "daily activities" subscore improved significantly more in the GC than L group at 1
198 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],

199 Cohen's *d* 1.14), and the "anxiety and depression" subscore improved significantly more in
200 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
201 "work and leisure activities" and the "social interest" subscores did not differ between groups
202 during follow-up. Likewise, the variation in Oswestry score did not differ between groups at 1
203 month (Supplementary Fig. S3). The groups did not differ in physical and mental component
204 summary scores of the SF-36 during follow-up (Supplementary Fig. S4).

205

206 Work status (Table 2)

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

212

213 Adverse effects

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

216

217 Discussion

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

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

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

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

241 Apart from technical concerns, we did not evidence side effects in the GC group,
242 which confirms the safety of soluble glucocorticoids for intradiscal injection. The hypothesis
243 that disc infection could explain part of active discopathy still remains controversial (22). No
244 antibiotic prophylaxis was proposed in the present study and no discitis was reported during
245 follow-up. In agreement with most previous studies of intradiscal injection of GCs
246 (9,13,23,24), the low-grade infection hypothesis seems unlikely.

247 NICE 2016 guidelines do not recommend intradiscal injections for chronic LBP (25).
248 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.

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

281

282 **Conclusion**

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

288

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296 the study's design, conduct, or reporting.

297

298 Figure Captions

299

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

301 **Figure 2.** Variation in low back pain (visual analog scale [VAS]) intensity. Data are mean

302 (SD). Visual analog scale (VAS) scores at weeks 1, 2 and 3 were self-reported by patients in

303 diaries, whereas VAS scores at 1, 3 and 6 months were completed during follow-up visits.

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

305

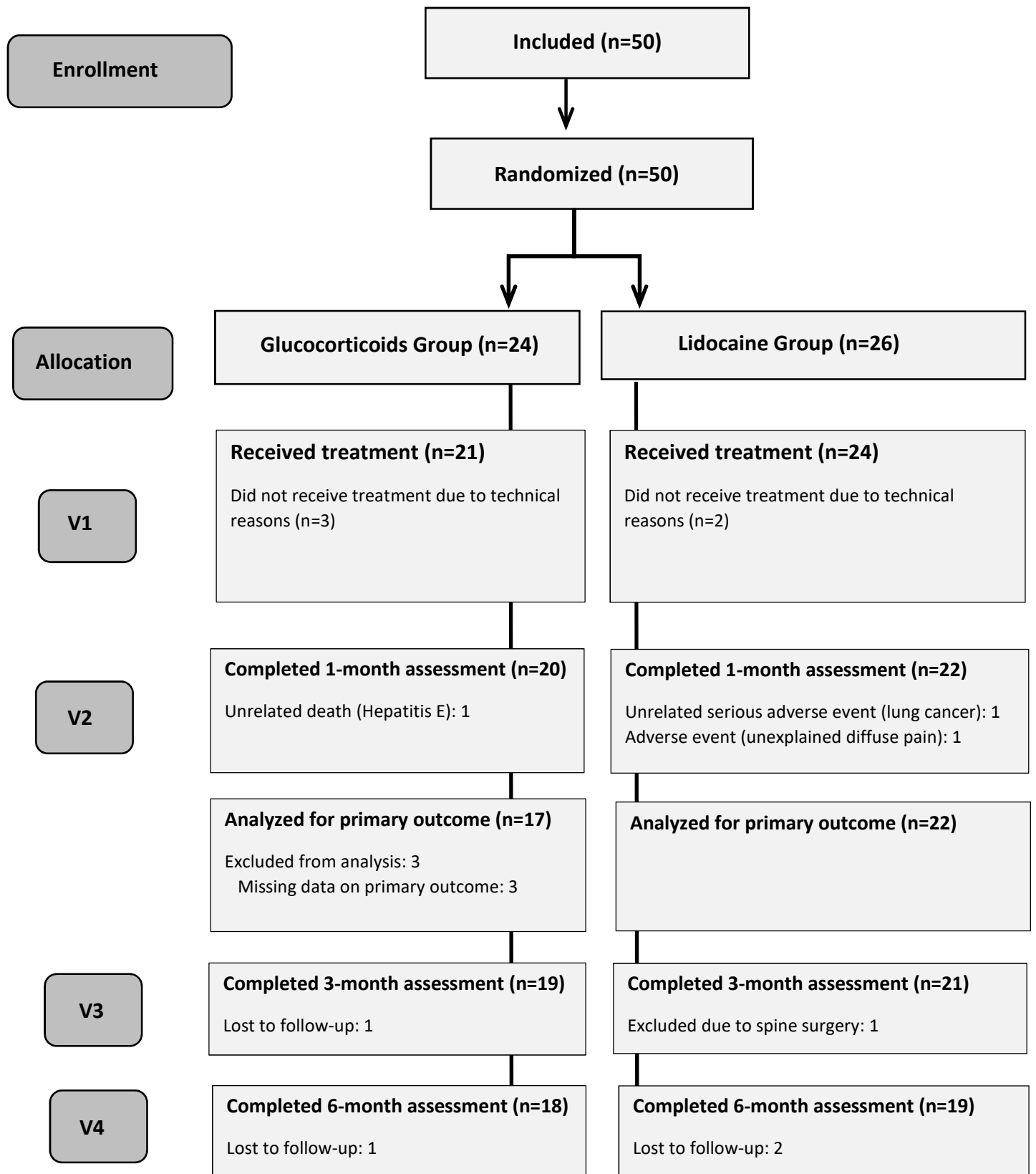
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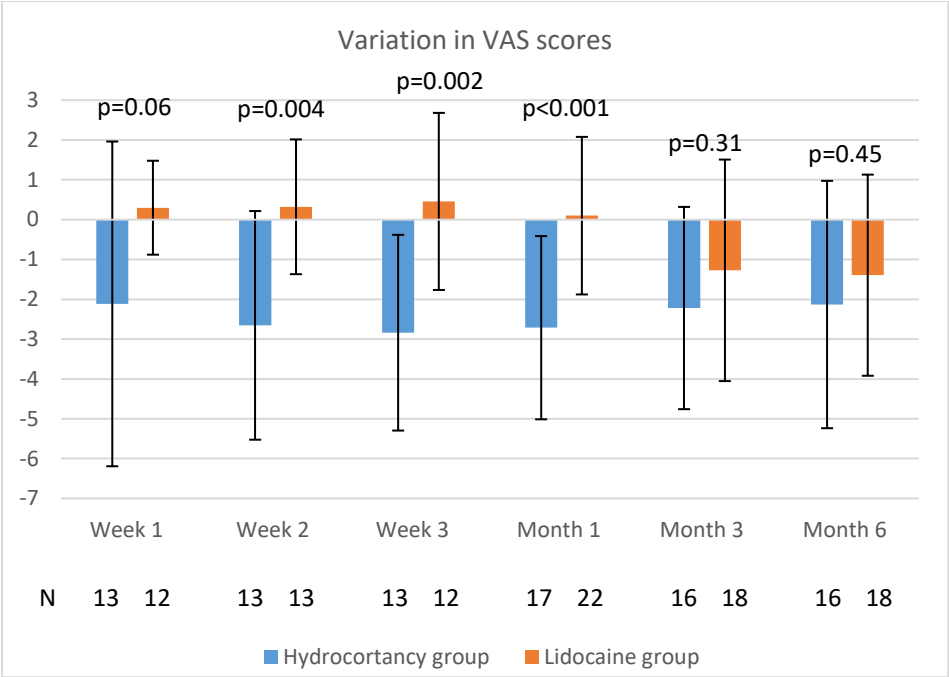
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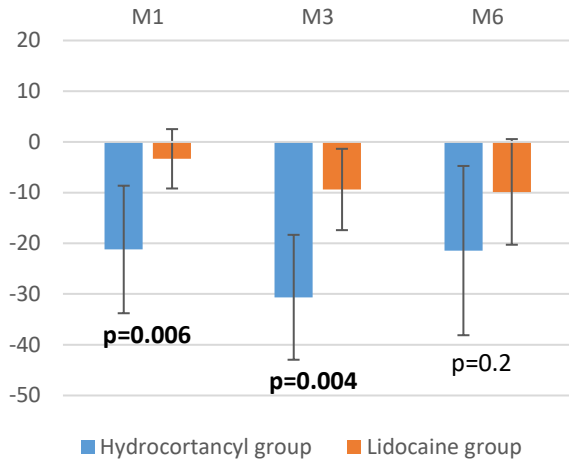
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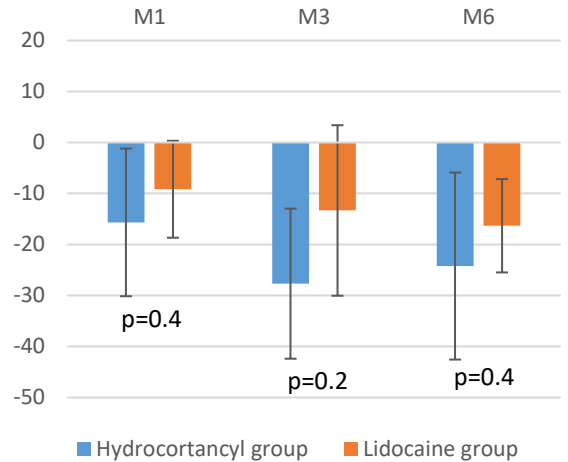




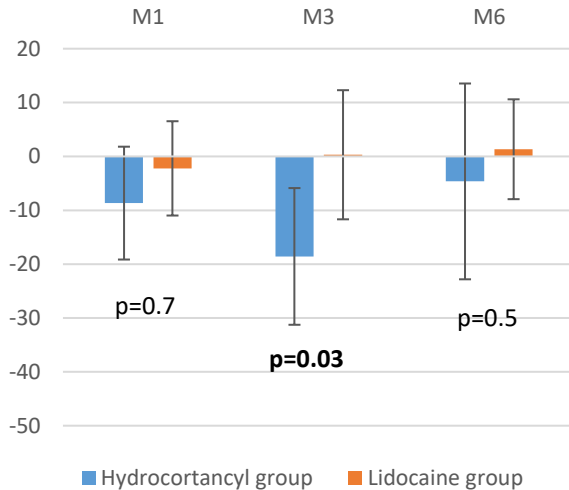
Daily activities



Work and leisure activities



Anxiety and depression



Social interest

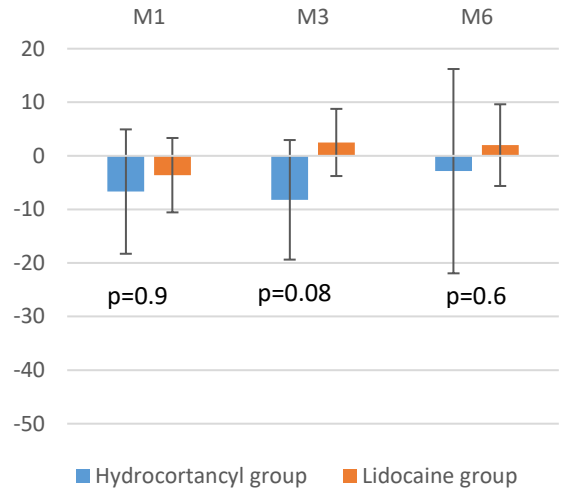


Table 1. Baseline characteristics of the population.

	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		
Antalgiics		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).