Higgins *et al.*
Anesthesiology and Perioperative Science (2024) 2:32
https://doi.org/10.1007/s44254-024-00069-z

Anesthesiology and Perioperative Science

ORIGINAL RESEARCH

Open Access

Retrospective study of the efficacy of methylprednisolone vs. triamcinolone in lumbar epidural steroid injections for the treatment of low back pain due to degenerative disc disease

Zachary R. Higgins[1,3], Shuchita Garg[1], Timothy Burroughs[1,4], Katherine A. Qualls[1,2], Jun-Ming Zhang[1] and Judith A. Strong[1*]

Abstract

Objective A common low back pain treatment is epidural injection of corticosteroids. The nominal target of anti-inflammatory corticosteroid drugs is the glucocorticoid receptor (GR). In vitro studies show many clinically used steroids also activate the mineralocorticoid receptor (MR) with substantial potency. Based on preclinical studies, this may have pro-inflammatory and pro-nociceptive effects that counter the desired GR effects. Of two outpatient pain clinics associated with the University of Cincinnati Department of Anesthesiology, one primarily used methylprednisolone while the other used mainly triamcinolone for epidural steroid injections. We hypothesized that triamcinolone would give better outcomes because in vitro, ratio of MR/GR potency is about 10 fold less favorable for methylprednisolone.

Methods We conducted a retrospective chart review of adults receiving lumbar epidural steroid injection for low back pain due to degenerative disc disease at the two pain clinics. For subjects treated at the first clinic, we obtained basic demographics, smoking history, 2 primary outcomes (patient-rated percent improvement in pain levels, and injection outcome rated as poor, partial, or good), and pain ratings (0–10 scale) before and after injection. For analysis, a subset of subjects from the second clinic was matched as closely as possible (sex, age, race, and ethnicity) to those from the first clinic.

Results Eighty-six subjects from the first clinic were identified, of whom fifty-five met inclusion criteria. Review of 83 potentially matched subjects from the second clinic yielded 37 subjects. From this combined set of subjects, 44 receiving triamcinolone and 48 receiving methylprednisolone were obtained. Matching was effective in avoiding significant differences between the two drug groups in age, weight, sex, race, and body mass index, however, the incidence of smoking (current and former) was significantly higher in the methylprednisolone group (who were primarily from clinic 1). The injection responses codified on a 0–2 scale, where 0 indicated a poor response, 1 a partial response with a second injection recommended, and 2 a good response where no further treatment was recommended at the 1 month follow up point, were not significantly different between the groups (Mann–Whitney,

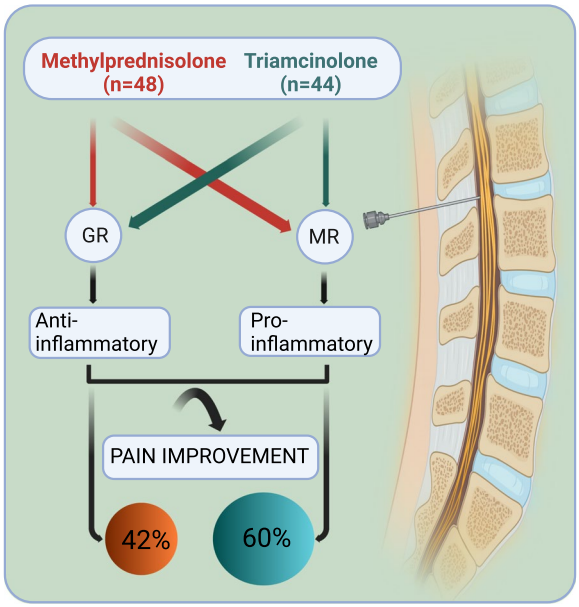
*Correspondence:
Judith A. Strong
judith.strong@uc.edu
Full list of author information is available at the end of the article

$p = 0.44$) although the triamcinolone group overall had slightly better responses. However, the patient-reported percent improvement after the injection was significantly better for the triamcinolone than for methylprednisolone (60% ± 5.3 vs. 42% ± 4.9), as was the pain ratings (0–10 scale) after the injection (5.0 ± 0.5 vs. 6.3 ± 0.3). A marked demographic difference between the two clinics in smoking rates was not controlled for in subject matching but accounting for smoking status did not affect the observed differences between the two steroids.

Conclusions Differences in the two primary outcomes, patient-reported percent improvement and pain ratings after epidural steroid injection, were consistent with the hypothesis that more GR-selective steroids may give better outcomes though the differences were modest. We propose that one factor in choosing steroids should be their relative potency in also activating the pro-inflammatory mineralocorticoid receptor.

Keywords Mineralocorticoid receptor, Epidural steroid, Low back pain, Smoking

Graphical Abstract



1 Introduction

Low back pain is an overwhelmingly common ailment experienced by over 80% of the adult population at some point in their lifetime. This symptom can result from many different causes (e.g., arthritis, disc problems, stenosis, inflammatory disorders, cancer, muscle problems, infection), although often the cause cannot be identified [1]. Acute low back pain (not further defined by cause) becomes chronic (lasting longer than 6 months) in up to 50% of patients deemed high-risk in a recent study based in primary care centers [2]. Local inflammation in the region of the lumbar sensory ganglia plays a role in many forms of low back pain, including those involving pathology of the intervertebral discs [3, 4]. A common treatment for some forms of low back pain is local injection of corticosteroids. Randomized clinical trials have provided sometimes conflicting results as summarized in recent reviews and meta-analyses of clinical trials of epidural steroid injections for lumbosacral radicular pain [5, 6]. There are fewer studies comparing the efficacy of the different steroids used.

The nominal target of anti-inflammatory corticosteroid drugs is the glucocorticoid receptor (GR). However, in vitro studies show that many clinically used steroids (including those commonly used for back pain, e.g., methylprednisolone and triamcinolone) can also activate the mineralocorticoid receptor (MR) with significant potency [7, 8]. The MR was originally viewed primarily as the target of aldosterone, promoting sodium reabsorption in the kidney. However, this receptor has been

detected in other cell types including peripheral sensory neurons [9]. In many non-renal tissues, MR activation is pro-inflammatory [10, 11]. Preclinical studies generally show that, in dorsal root ganglion (DRG) neurons, GR is anti-nociceptive and MR is pro-nociceptive [12–15], including in a low back pain model [16, 17]. In another low back pain model, more GR-selective drugs, or a combination of clinically used steroids with MR blockers, more effectively improved pain behaviors, including local actions at the level of the sensory ganglia [9, 18, 19].

We conducted a retrospective chart review study of adult patients receiving lumbar epidural steroid injection for low back pain, with a diagnosis of degenerative disc disease, at two outpatient pain clinics affiliated with the Department of Anesthesiology at the University of Cincinnati College of Medicine. During the time period studied, one clinic mainly used methylprednisolone (Depo Medrol™) while the other used mainly triamcinolone (Kenalog™), based on differing preferences of the physicians staffing the two clinics at the time. Our hypothesis was that triamcinolone would give better outcomes than methylprednisolone, as the ratio of MR potency to GR potency is about 10-fold less favorable for methylprednisolone. In one in vitro study, the GR/MR half maximal effective concentration (EC50) ratio was 1.3 for methylprednisolone and 0.12 for triamcinolone, where a ratio of 1 indicates equal potency at both receptors and lower numbers indicate higher GR selectivity [8].

2 Methods

The protocol for conducting the study was approved by the Institutional Review Board of the University of Cincinnati (protocol number 2017–2240) and included a Health Insurance Portability and Accountability Act waiver for retrospective review of chart records without obtaining individual informed consent forms.

The Department of Anesthesiology at the University of Cincinnati College of Medicine had two associated outpatient clinics from which subjects were drawn retrospectively. Clinic 1 was located near our urban medical school while clinic 2 was suburban. Patients who had received lumbar epidural steroid injections during the period 8/1/15 through 8/31/17 at the two clinics were automatically extracted from the electronic health care records for review. The clinic providers' criteria for recommending a patient for a lumbar epidural steroid injection are generally acute-on-chronic or chronic low back pain, often with radicular symptoms down the lower extremity/ies, and usually accompanied by a diagnosis of lumbar degenerative disc disease, lumbar spinal stenosis, or disc herniation. In this study we restricted analysis to those subjects with a diagnosis of degenerative disc disease, in order to reduce the variability of the study population. Injections were performed by attending physicians or pain fellows (seven different providers in all). The standard protocol for doing the epidural steroid injection was used: after needle placement under fluoroscopic guidance, 80 mg of triamcinolone or methylprednisolone in 1–2 cc of normal saline was injected using a midline interlaminar approach. These are considered equivalent glucocorticoid doses in clinical practice [20] although in vitro experiments with a reporter gene show greater potency at the GR for methylprednisolone (EC50 = 2.9 nM) compared to triamcinolone (EC50 = 34.2 nM) [8]. We did not observe any major complications, consistent with previous reports about the very low incidence of catastrophic outcomes which must be considered in deciding to perform an epidural steroid injection [21]. The study was not designed to capture minor side effects accurately.

Subjects from clinic 1, that predominately received methylprednisolone, were reviewed based on the following.

Inclusion criteria were:

- age 18 or over
- received either methylprednisolone or triamcinolone lumbar epidural steroid injections
- diagnosis of degenerative disc disease

Exclusion criteria were:

- under age 18
- having surgery for low back pain conditions prior to their epidural injection
- previous lumbar epidural steroid injection within the past year but before the time period defined for our search (i.e., within the year just prior to 8/1/15)
- no follow-up visits after their first epidural steroid injection
- members of vulnerable populations as indicated in their medical records (e.g., pregnant, prisoners, cognitively impaired, employees or students of the university, and wards of the state)

The exclusion for previous epidural steroid injection within one year enabled us to treat the earliest injection as a "first injection" and to determine whether additional injections were administered. There were fewer subjects at the first clinic than at the second, and the populations served by the two clinics differ substantially, so a subset of subjects from the second clinic was matched as closely as possible for sex, age (closest available match, 3 pairs of subjects differed by 1 to 4 years in age while other pairs differed by less one year of age), race, and ethnicity to

those included from the first clinic, and selected for analysis. Where multiple matches were available the match with closest body mass index (BMI) was used. However, it was not always possible to obtain a match. In addition, a small number of patients from the first clinic were given triamcinolone instead of methylprednisolone and vice versa.

Data obtained from the electronic health record for subjects meeting inclusion/exclusion criteria included: age, sex, race, ethnicity, height, weight, BMI, smoking history, comorbidities present at the time of the injection, presence or absence of radicular symptoms, patient-rated percent improvement in their pain level, injection outcome, and pain ratings (0–10) before and after injection. These estimates of pain ratings and percent improvement were obtained from records of the follow-up visit after the injection, most of which occurred in a 4–6 week framework as part of the standard practice at the clinics. Because the most uniformly recorded information at the follow-up visit were the percent improvement and pain ratings, these were the primary outcomes analyzed. For percent improvement, patients were simply asked their estimate of the overall percent improvement in pain levels since before the injection. The pain ratings were obtained just prior to injection and at the follow-up visit, and hence were more of an "at the moment" measure. The injection outcome at the follow-up visit was also codified as: 0, poor response to injection, alternative treatment recommended; 1, partial response to injection so a second injection was recommended; or 2, good response to injection so no further injections immediately recommended, based on the clinical advice recorded during the follow-up visit. Data was also obtained about whether additional injections were performed in the time period examined and if so, what their outcome was. Analysis was focused on the first identified injection with the exception of analysis of time to a second injection.

Data was analyzed using Prism 9 and 10 (GraphPad Software, Boston, MA, USA). Comparisons between groups were performed using Fisher's exact test or chi square test for categorical data; t-test or Mann–Whitney test, as appropriate based on D'Agostino & Pearson test for normality for continuous data; and Mann–Whitney test for ordinal data. Where multiple factors or before-and-after data were analyzed, two-way repeated measures analysis of variance (ANOVA) was used, as indicated. Factors were also analyzed using multiple linear regression (least squares method) with percent improvement at the follow-up visit as the outcome. Values are presented as mean ± SEM (standard error of the mean), unless otherwise indicated. Significance was ascribed for $p < 0.05$.

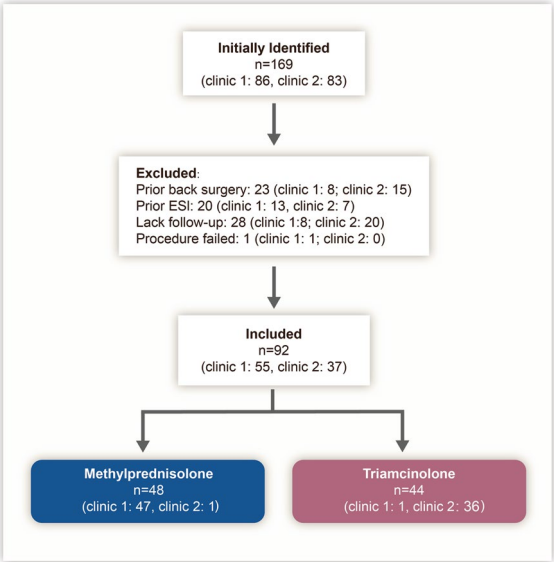


Fig. 1 Study Flow. Diagram indicates the number of subjects initially identified (clinic 1) as having lumber epidural steroid injections, or identified with subject matching from clinic 2, along with exclusions and final numbers analyzed from each clinic and drug group

3 Results

We identified 86 subjects from clinic 1 who had received epidural steroid injections. After excluding those not meeting all criteria 55 remained (Fig. 1). Attempts to match the remaining subjects with subjects from clinic 2 based on sex, age, race, and ethnicity yielded 83 subjects, of which 37 remained after reviewing for exclusion. For some subjects no match was available, even when allowing age differences of up to 3 years. Some inconsistencies in the coding of race and ethnicity were noted in the medical records, and ethnicity was not further considered.

Subjects were then divided into methylprednisolone and triamcinolone groups. The partial subject matching was effective in avoiding significant differences between the groups in age, weight, sex, and race (Table 1). BMI also did not differ between groups. However, the incidence of smoking (current and former) was significantly higher in the methylprednisolone group (who were primarily from clinic 1). We examined other common comorbidities noted during the chart review: type 2 diabetes (20% of all subjects); hypertension (18%); the rates of these as well as the incidence of radicular symptoms (77%) did not differ significantly between the two groups (Table 1). Many other comorbidities were noted but, individually, were too rare to examine in any detail. Some of these were combined into general classes, for

Table 1 Comparison of demographic and clinical variables between the 2 drug groups. *SD* standard deviation

		Triamcinolone	Methylprednisolone	*p*-value
N		44	48	
Age	mean ± SD, years	54.8 ± 12.1	51.9 ± 14.5	0.3[a]
BMI	mean ± SD, kg/m^2	32.3 ± 8.1	33.7 ± 7.4	0.25[b]
Weight	mean ± SD, kg	93.4 ± 26.1	93.4 ± 23.0	0.80[b]
Race	Caucasian	18	19	0.56[c]
	African American	24	24	
	Other	2	5	
Sex	Female	28	33	0.66[d]
	Male	16	15	
Smoking status	Current	12	21	< 0.0001[c]
	Former smoker	5	19	
	Never smoker	27	8	
Diabetic	yes	8	10	0.80[d]
	no	36	38	
Hypertension	yes	11	6	0.18[d]
	no	33	42	
Additional pain condition	yes	19	24	0.54[d]
	no	25	24	
Additional spine condition	yes	8	7	0.78[d]
	no	36	41	
Additional joint condition	yes	12	16	0.65[d]
	no	32	32	
Radicular pain	yes	32	33	0.61[d]
	no	8	11	
	unknown	4	4	
Pain duration	mean ± SD, years	8.3 ± 6.4	8.2 ± 8.6	0.38[b]
Patient rated improvement	mean ± SD, %	60.5 ± 33.4	42.5 ± 35.0	0.01[b]
Injection outcome	0 poor	14	20	0.43[b]
	1 partial	13	13	
	2 good	16	15	
Pain rating, before	mean ± SD	7.0 ± 2.1	7.5 ± 1.5	0.61[e]
Pain rating, after	mean ± SD	5.0 ± 3.0	6.5 ± 2.2	0.003[e]
Time to 2nd injection	mean ± SD, weeks	24.5 ± 18	15.8 ± 9	0.11[a]
		(*n* = 14)	(*n* = 15)	

[a] t-test

[b] Mann–Whitney

[c] Chi-square

[d] Fisher's exact test

[e] Two-way ANOVA

which the incidence also did not differ between the two groups, including: presence of additional pain conditions not related to low back pain (47% of subjects, most commonly osteoarthritis and myofascial pain); spine conditions in addition to degenerative disc disease (16% of subjects, most commonly sacroiliac joint pain and spondylosis); presence of another condition affecting the joints (30% of subjects; most commonly sacroiliac joint pain and spondylosis). The duration of pain did not differ significantly between the two groups.

When the results of the injection were codified as 0 (poor response to injection, alternative treatment recommended); 1 (partial response, a second injection was recommended); or 2 (good response to injection, no immediate further injections recommended), the distribution of responses did not differ significantly between the groups (Fig. 2A and Table 1; Mann–Whitey test,

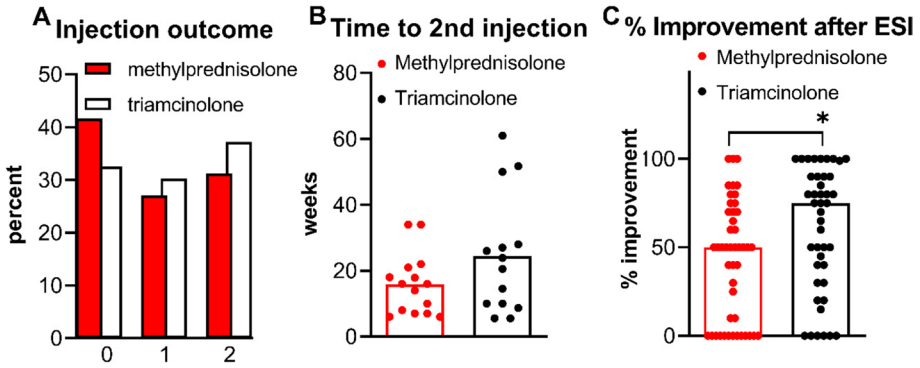


Fig. 2 Injection outcomes as a function of drug used. **A** Distribution of injection outcomes codified as 0 (poor) to 2 (good). Median score did not differ between the groups (Mann–Whitney, $p=0.43$). **B** Weeks until a second injection in those subjects who were given one. Scatterplot of individual data; bars indicate mean. Average weeks to a second injection did not differ between the 2 groups ($p=0.11$, t-test), $N=15$ methylprednisolone and 14 triamcinolone subjects who received second injections. **C** Subject ratings of percent improvement after their epidural steroid injection (ESI). Data is presented as scatterplot of individual values, bars indicate median. *, $p<0.05$, Mann–Whitney test

$p=0.43$) although the percentage of better outcomes was slightly higher in the triamcinolone group. The percentage of subjects with a record of receiving a second injection was not different between the two groups (31% for methylprednisolone, 32% for triamcinolone, Fisher's exact test, $p>0.99$). The number of weeks until the next injection, for those that received a second injection, seemed higher in the triamcinolone group but this difference did not reach significance (Fig. 2B and Table 1).

However, one of the primary outcomes, patient ratings of percent improvement in pain levels provided at the follow-up visit after their injection, was significantly higher in the triamcinolone group (Fig. 2C and Table 1). This result had an observed effect size of 0.53 (considered medium), and power of 71% in post-hoc analysis.

As the other primary outcome, pain ratings (0–10 scale) were obtained just prior to the epidural steroid injection, and again at the follow-up visit. Two-way repeated measures ANOVA analysis (Fig. 3 and Table 1) showed that pain ratings did not differ between the 2 groups before the injection. Both groups showed significant improvements in pain ratings after the injections, but the post-injection ratings were significantly higher (more pain) in the methylprednisolone group.

Because there were significant differences between the groups in smoking incidence, we conducted secondary analysis to see if this factor might contribute to the apparent difference between the two steroids. Combining subjects into two groups, current smokers and current nonsmokers (including former smokers) regardless of steroid used, two-way repeated measures ANOVA analysis showed that there was a strong trend towards an overall effect of smoking on pain ratings (higher in smokers, $p=0.067$), but that the epidural injections still significantly reduced pain ratings in both groups (Fig. 4A).

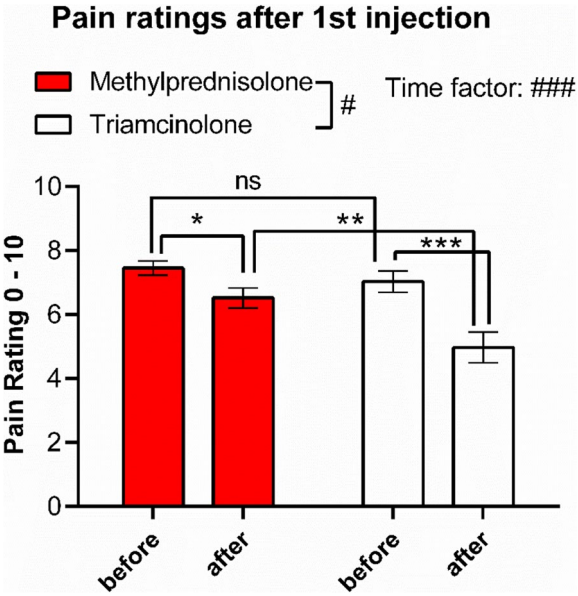


Fig. 3 Effect of drug type on pain ratings obtained just before and at follow-up after the epidural steroid injections. Average pain ratings ± SEM are shown. #, $p<0.05$; ###, $p<0.001$, significant overall effect of time factor (injection) and type of drug injected, 2-way repeated measure ANOVA; $F(1,82)=92.8$ for time factor, 5.88 for drug factor. n.s., not significant; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$, significance of indicated posthoc comparisons, Šídák's multiple comparisons test

The subject-reported percent improvement values when analyzed with subjects divided into current smoker and nonsmoker groups, still demonstrated a difference between methylprednisolone and triamcinolone, but did not show an overall effect of smoking status (Fig. 4B).

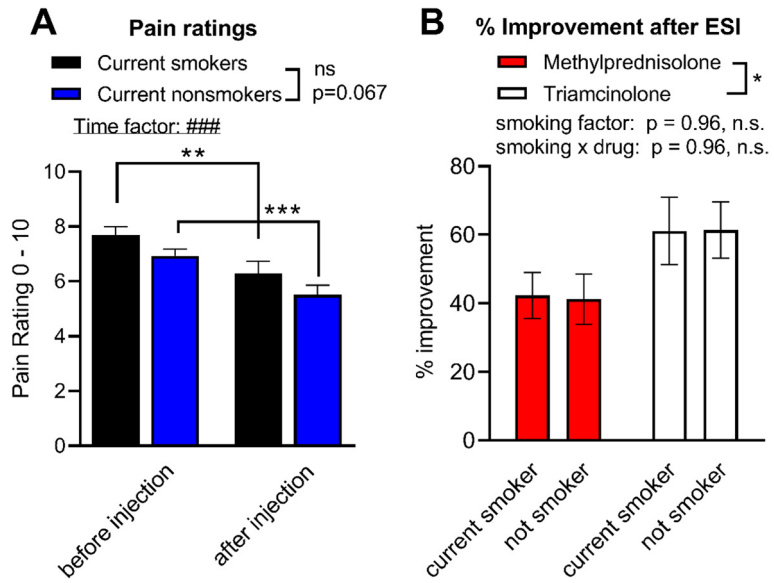


Fig. 4 Interaction of smoking status with injection responses. **A** Average pain ratings ± SEM are shown. n.s., not significant; ###, $p < 0.001$, significant overall effect of time factor (injection) and smoking status, 2-way repeated measures ANOVA, F(1,86) = 81.8 for time factor, 3.45 for smoking factor. *p*-value for their interaction was 0.94. n.s., not significant; **, $p < 0.01$; ***, $p < 0.001$, significance of indicated posthoc comparisons, Šídák's multiple comparisons test. $N = 32$ current smokers and 56 never or former smokers for whom both before and after pain ratings were available. **B** Interaction of smoking status with steroid used in percent improvement ratings. Subjects were divided into current and nonsmokers within each drug group. Average percent improvement ratings ± SEM are shown. *, $p < 0.05$, n.s., not significant, two-way ANOVA, F(1,72) = 5.1 for drug factor, 0.002 for smoking factor, 0.006 for interaction

Table 2 Analysis of comorbidities with multiple linear regression models

Factors included in model	*p*-value for overall fit	individual factors with $p < 0.11$
All models: Sex, race, BMI, drug	0.04	Drug (0.02)
plus current smoking status	0.054	Drug (0.01); BMI (0.10)
plus radiculopathy factor	0.02	Drug (0.02); radiculopathy (0.11)
plus smoking and radiculopathy	0.03	Drug (0.01); radiculopathy (0.08)
plus additional pain condition	0.07	Drug (0.01)
plus additional spine condition	0.02	Drug (0.01); spine condition (0.07)
plus additional joint condition	0.053	Drug (0.018)
plus hypertension	0.06	Drug (0.02)
plus diabetes	0.06	Drug (0.01)
plus pain duration	0.02	Drug (0.049); BMI (0.03)

When a multiple linear regression model incorporating BMI, sex, race, and drug used was fit to predict the percent improvement at follow-up, the overall regression was significantly better than a null model ($p = 0.04$) and the drug factor was the only individual factor that reached significance. Adding the clinical comorbidities indicated in Table 1, individually, generally gave similar overall regression probabilities, though in some cases the probabilities were no longer significant (though still < 0.1) (Table 2). Separate analysis of the radiculopathy factor and drug interaction (as done for smoking) did not confirm a significant effect of radiculopathy or drug-radiculopathy interaction. In the main, the regression analysis suggested a trend towards an effect of some of the comorbidities examined but the primary finding was the robustness of the superiority of triamcinolone which remained significant even when we took into account these other comorbidities.

As shown in Table 2, the indicated comorbidities (see Table 1) were added individually to the basic model that incorporated sex, race, BMI, and drug used to predict percent improvement. Only individual probability values

with $p < \sim 0.1$ are included. Direction of effects or trends were for higher percent improvement for: triamcinolone over methylprednisolone; no radiculopathy; no additional spine condition; higher BMI.

4 Discussion

In this study, we compared the outcomes of lumbar epidural steroid injections for low back pain associated with degenerative disc disease, between subjects receiving triamcinolone or methylprednisolone. Our study took advantage of the fact that clinicians at different outpatient pain clinics associated with our anesthesiology department, happened to prefer different steroids for treatment. We hypothesized that triamcinolone would give better outcomes than methylprednisolone based on in vitro studies showing that the latter is more potent at also activating the pro-inflammatory MR. Some of our outcome measures (pain ratings, subject reported percent improvement in pain levels) were consistent with this hypothesis, while others (outcome codified on a 0–2 scale, number of weeks until a second injection was needed) showed no significant difference between the two drugs.

There have been a number of studies seeking to examine the efficacy of epidural steroids for low back pain. The procedure has remained somewhat controversial despite decades of use although many studies show a modest improvement in pain outcomes (e.g., [5]). Most meta-analyses and even some individual studies group subjects together that received different steroids, making it difficult to test our hypothesis with data from prior studies. One study comparing methylprednisolone with triamcinolone for painful shoulder calcific tendinopathy [22] showed evidence for superiority of triamcinolone, while another study comparing the 2 drugs in rheumatoid arthritis or spondyloarthritis of the knee found no difference [23]. As our hypothesis is based on the effects of steroids on sensory neurons, conditions not involving direct inflammation near the DRG may not be appropriate tests of the hypothesis. For example, some actions of steroids might be on GR expressed in peripheral immune cells. A retrospective study comparing dexamethasone, triamcinolone, and betamethasone used to treat lumbosacral radiculopathy found no differences between the drugs in pain scores or number of injections [24]; in this study the analysis compared particulate steroids (i.e., combined triamcinolone (30%) and betamethasone (18%) subjects as receiving particulate) to those receiving nonparticulate dexamethasone (52%). However, as the GR selectivity of dexamethasone is similar to that of triamcinolone, while that of betamethasone is even more favorable, (GR/MR EC50 ratio of 0.02), this study could not be used to test our hypothesis. A number of studies have compared various particulate steroids with nonparticulate steroids (e.g., [25–28]) with the soluble steroid being dexamethasone. These studies have had somewhat mixed results. However, these studies also cannot serve as good tests of our hypothesis in that dexamethasone has a GR selectivity profile that is similar to that of e.g., triamcinolone [8] which was the comparator in several of these studies. We note that in our study, the superiority of triamcinolone over methylprednisolone for some outcomes is the opposite of what would be predicted from the premise that more particulate steroids will give longer lasting results than more soluble steroids, since methylprednisolone is the more particulate of the two. However, differences in duration of action of the two steroids could have also contributed to our findings.

One limitation of our study is that analysis was confined to relatively early time points, generally 4–6 weeks after the epidural injection, a clinically based time that was not strictly defined due to the retrospective design of the study. However, we would still expect to see differences between the two steroids examined insofar as our hypothesis focuses directly on the role of MR and GR in sensory neurons that give rise to pain signals. In these neurons, benefits of reduced MR activation should be evident even at early time points. Our study and many of the above cited studies provide evidence for reductions in pain attributed to epidural steroid injections, but these effects are modest and incomplete. A reduction of about 2 points on 10-point pain scales, such as we observed, is remarkably consistent with the values obtained in most of the studies cited here. Hence, there is room for improvement in this treatment modality. We suggest that considering the role of the MR is one element of improving low back pain treatment. We note that preclinical studies about the effects of MR activation in sensory neurons suggest that even a highly GR-selective steroid's actions might be improved by concomitant MR block, as inflammatory conditions near the DRG can also activate MR (e.g., [9]), including by the local production of endogenous aldosterone (e.g., [13, 15]). Epidural injections may also act at the spinal cord, where preclinical studies also suggest a pro-nociceptive role for the MR [15]. Although specific MR blockers that are FDA-approved for other indications exist, such as spironolactone, the second generation, more selective antagonist eplerenone, and the recently approved third generation antagonists finerenone and esaxerenone [29, 30], none to our knowledge are available in forms suitable for epidural injection. Another approach that might help improve the efficacy of clinical steroids is to examine how they are activated or inactivated by steroid-metabolizing enzymes, many of which are also present locally within the DRG [17,

31–33] and, in a preclinical study, were upregulated by local DRG inflammation [34].

A second limitation of our study is the fact that the subjects receiving methylprednisolone and triamcinolone were largely drawn from either an urban or suburban practice, respectively. The two clinics serve very different populations. For example, the first clinic generally has lower income clients. This may have effects on health outcomes that were not controlled by our largely successful attempt to match subjects based on age, race, and sex. Indeed, the observed higher incidence of smoking in the methylprednisolone group is consistent with observations that smoking incidence is higher in lower income groups since the different incidence of current smoking in the two drug groups (27%, triamcinolone; 44% methylprednisolone) was largely reflecting the difference between the two clinics (45% at clinic 1, 22% at clinic 2) [35]. The trend (Fig. 4A; $p=0.067$) in our data indicating higher pain levels in smokers is also consistent with previous studies including in low back pain patients and is likely due to a complex interplay of causative factors [36]. Nevertheless, our findings of outcomes being better after triamcinolone than methylprednisolone remained after considering the current smoking status of the subjects. We also could not attribute the difference between the two drug groups to common comorbidities, which did not differ between the groups, including diabetes, hypertension, and presence of other pain, spine, and joint conditions. However, due to the retrospective nature of the study and the relatively small sample size, the data on these comorbidities was likely not of high quality, being limited to those noted in the medical record at the time of the epidural steroid injections, in turn likely dependent on the varying record-taking habits of the different practitioners. We also observed a trend towards the presence of radicular symptoms predicting a worse outcome on the patient-reported percent improvement ratings. We have experienced recent changes in insurance company practices to approve epidural steroid injections only when these symptoms are present, although the data obtained largely pre-dated this shift. Despite the limitations of our comorbidity data, the finding of superior outcome with triamcinolone compared to methylprednisolone was robust even when comorbidities were individually considered.

5 Conclusion

This retrospective chart review showed that triamcinolone gave modestly better outcomes than methylprednisolone in some patient-reported pain measures after epidural steroid injection for low back pain in subjects with degenerative disc disease. We suggest that the modest efficacy of epidural steroid injections could be improved by considering the MR activation profile of various steroids, which has been largely ignored in most clinical studies.

Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index
DRG	Dorsal root ganglion
EC50	Half maximal effective concentration
GR	Glucocorticoid receptor
MR	Mineralocorticoid receptor

Acknowledgements

This work was warmly supported by the Department of Anesthesiology, University of Cincinnati.

Author contributions

Conducted chart review: ZRH, SG, TB. Data analysis: ZRH, KQ, JAS. Experimental design and supervision: SG, TB, J-MZ, JAS. Drafted manuscript: JAS. Edited manuscript: ZRH, SG, KQ, J-MZ, JAS.

Availability of data and materials

All deidentified data pertaining to the study are available on the University of Cincinnati's public data repository, Scholar@UC (https://scholar.uc.edu/show/nc580p28v), for a period of 5 years following publication.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the University of Cincinnati 2017–2240 and included a HIPPA waiver for retrospective review of chart records without obtaining individual informed consent forms.

Consent for publication

All authors gave their content for publication.

Competing interests

The authors have no conflicts of interest to disclose.

Author details

[1]Department of Anesthesiology, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA. [2]Graduate Program in Molecular, Cellular and Biochemical Pharmacology, University of Cincinnati, Cincinnati, OH 45220, USA. [3]Present Affiliation: Department of Neurology, Anschutz Medical Center, University of Colorado, Denver, CO 80045, USA. [4]Present Affiliation: St. Elizabeth Hospital, Spine and Pain Clinic, Florence, KY 41042, USA.

Received: 1 May 2024 Revised: 8 August 2024 Accepted: 9 August 2024
Published online: 06 September 2024

References

1. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. Lancet. 2018;391(10137):2356–67.
2. Delitto A, Patterson CG, Stevans JM, Freburger JK, Khoja SS, Schneider MJ, et al. Stratified care to prevent chronic low back pain in high-risk patients: the TARGET trial. A multi-site pragmatic cluster randomized trial. EClinicalMedicine. 2021;34:100795.
3. Kallewaard JW, Terheggen MA, Groen GJ, Sluijter ME, Derby R, Kapural L, et al. 15. Discogenic low back pain. Pain Pract. 2010;10(6):560–79.
4. Ross JS. Non-mechanical inflammatory causes of back pain: current concepts. Skeletal Radiol. 2006;35(7):485–7.
5. Manchikanti L, Knezevic E, Latchaw RE, Knezevic NN, Abdi S, Sanapati MR, et al. Comparative systematic review and meta-analysis of Cochrane review of epidural injections for lumbar radiculopathy or sciatica. Pain Physician. 2022;25(7):E889–916.

6. Oliveira CB, Maher CG, Ferreira ML, Hancock MJ, Oliveira VC, McLachlan AJ, et al. Epidural corticosteroid injections for lumbosacral radicular pain. Cochrane Database Syst Rev. 2020;4(4):CD013577.
7. Sedlak D, Paguio A, Bartunek P. Two panels of steroid receptor luciferase reporter cell lines for compound profiling. Comb Chem High Throughput Screen. 2011;14(4):248–66.
8. Grossmann C, Scholz T, Rochel M, Bumke-Vogt C, Oelkers W, Pfeiffer AF, et al. Transactivation via the human glucocorticoid and mineralocorticoid receptor by therapeutically used steroids in CV-1 cells: a comparison of their glucocorticoid and mineralocorticoid properties. Eur J Endocrinol. 2004;151(3):397–406.
9. Dong F, Xie W, Strong JA, Zhang J-M. Mineralocorticoid receptor blocker eplerenone reduces pain behaviors in vivo and decreases excitability in small diameter sensory neurons from local inflamed dorsal root ganglia in vitro. Anesthesiology. 2012;117(5):1102–12.
10. Brown NJ. Aldosterone and end-organ damage. Curr Opin Nephrol Hypertens. 2005;14(3):235–41.
11. Funder JW. Aldosterone, mineralocorticoid receptors and vascular inflammation. Mol Cell Endocrinol. 2004;217(1–2):263–9.
12. Tafelski S, Mohamed D, Shaqura M, Assaf C, Beyer A, Treskatsch S, et al. Identification of mineralocorticoid and glucocorticoid receptors on peripheral nociceptors: translation of experimental findings from animal to human biology. Brain Res. 2019;1712:180–7.
13. Sun YE, Peng L, Sun X, Bo J, Yang D, Zheng Y, et al. Intrathecal injection of spironolactone attenuates radicular pain by inhibition of spinal microglia activation in a rat model. PLoS One. 2012;7(6):e39897.
14. Shaqura M, Li X, Al-Khrasani M, Shakibaei M, Tafelski S, Furst S, et al. Membrane-bound glucocorticoid receptors on distinct nociceptive neurons as potential targets for pain control through rapid non-genomic effects. Neuropharmacology. 2016;111:1–13.
15. Gu X, Peng L, Yang D, Ma Q, Zheng Y, Liu C, et al. The respective and interaction effects of spinal GRs and MRs on radicular pain induced by chronic compression of the dorsal root ganglion in the rat. Brain Res. 2011;1396:88–95.
16. Shaqura M, Li L, Mohamed DM, Li X, Treskatsch S, Buhrmann C, et al. Neuronal aldosterone elicits a distinct genomic response in pain signaling molecules contributing to inflammatory pain. J Neuroinflammation. 2020;17:183.
17. Mohamed DM, Shaqura M, Li X, Shakibaei M, Beyer A, Treskatsch S, et al. Aldosterone synthase in peripheral sensory neurons contributes to mechanical hypersensitivity during local inflammation in rats. Anesthesiology. 2020;132(4):867–80.
18. Ye L, Xie W, Strong JA, Zhang JM. Blocking the mineralocorticoid receptor improves effectiveness of steroid treatment for low back pain in rats. Anesthesiology. 2014;121(3):632–43.
19. Ibrahim SIA, Xie W, Strong JA, Tonello R, Berta T, Zhang JM. Mineralocorticoid antagonist improves glucocorticoid receptor signaling and dexamethasone analgesia in an animal model of low back pain. Front Cell Neurosci. 2018;12:453.
20. Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's: the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill Education; 2011.
21. Cohen SP, Greuber E, Vought K, Lissin D. Safety of epidural steroid injections for lumbosacral radicular pain: unmet medical need. Clin J Pain. 2021;37(9):707–17.
22. Battaglia M, Guaraldi F, Gori D, Castiello E, Arvat E, Sudanese A. Efficacy of triamcinolone acetate and methylprednisolone acetonide for intrabursal injection after ultrasound-guided percutaneous treatment in painful shoulder calcific tendonitis: a randomized controlled trial. Acta Radiol. 2017;58(8):964–70.
23. Kumar A, Dhir V, Sharma S, Sharma A, Singh S. Efficacy of methylprednisolone acetate versus triamcinolone acetonide intra-articular knee injection in patients with chronic inflammatory arthritis: a 24-week randomized controlled trial. Clin Ther. 2017;39(1):150–8.
24. McCormick ZL, Cushman D, Marshall B, Caldwell M, Patel J, Ghannad L, et al. Pain reduction and repeat injections after transforaminal epidural injection with particulate versus nonparticulate steroid for the treatment of chronic painful lumbosacral radiculopathy. PM R. 2016;8(11):1039–45.
25. Lee GY, Lee JW, Lee E, Yeom JS, Kim KJ, Shin HI, et al. Evaluation of the efficacy and safety of epidural steroid injection using a nonparticulate steroid, dexamethasone or betamethasone: a double-blind, randomized, crossover, clinical trial. Korean J Pain. 2022;35(3):336–44.
26. El-Yahchouchi C, Geske JR, Carter RE, Diehn FE, Wald JT, Murthy NS, et al. The noninferiority of the nonparticulate steroid dexamethasone vs the particulate steroids betamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. Pain Med. 2013;14(11):1650–7.
27. Datta R, Upadhyay KK. A randomized clinical trial of three different steroid agents for treatment of low backache through the caudal route. Med J Armed Forces India. 2011;67(1):25–33.
28. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. Pain Med. 2006;7(3):237–42.
29. Rogerson FM, Yao Y, Smith BJ, Fuller PJ. Differences in the determinants of eplerenone, spironolactone and aldosterone binding to the mineralocorticoid receptor. Clin Exp Pharmacol Physiol. 2004;31(10):704–9.
30. Liu W, Yu S. Nonsteroidal mineralocorticoid receptor antagonist eliciting cardiorenal protection is a new option for patients with chronic kidney disease. Kidney Dis (Basel). 2023;9(1):12–25.
31. Li X, Shaqura M, Mohamed D, Beyer A, Yamada S, Mousa SA, et al. Pro-versus antinociceptive nongenomic effects of neuronal mineralocorticoid versus glucocorticoid receptors during rat hind paw inflammation. Anesthesiology. 2018;128(4):796–809.
32. Schaeffer V, Meyer L, Patte-Mensah C, Mensah-Nyagan AG. Progress in dorsal root ganglion neurosteroidogenic activity: basic evidence and pathophysiological correlation. Prog Neurobiol. 2010;92(1):33–41.
33. Schaeffer V, Meyer L, Patte-Mensah C, Eckert A, Mensah-Nyagan AG. Sciatic nerve injury induces apoptosis of dorsal root ganglion satellite glial cells and selectively modifies neurosteroidogenesis in sensory neurons. Glia. 2010;58(2):169–80.
34. Strong JA, Xie W, Coyle DE, Zhang JM. Microarray analysis of rat sensory ganglia after local inflammation implicates novel cytokines in pain. PLoS One. 2012;7(7):e40779.
35. Centers for Disease Control and Prevention [Internet]. Burden of Cigarette Use in the U.S. 2023- [cited 2024 Apr 28]. Available from: https://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-united-states.html.
36. Ditre JW, Brandon TH, Zale EL, Meagher MM. Pain, nicotine, and smoking: research findings and mechanistic considerations. Psychol Bull. 2011;137(6):1065–93.

Publisher's Note