Efficacy and Safety of Lumbar Epidural Dexamethasone Versus Methylprednisolone in the Treatment of Lumbar Radiculopathy

A Comparison of Soluble Versus Particulate Steroids

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Introduction: The literature is limited in the comparative efficacy and safety of dexamethasone phosphate (DP) compared with methylprednisolone acetate (MPA) in the treatment of lumbar radiculopathy by epidural injection. This study attempts to test the hypothesis that 2 corticosteroids are equivalent in efficacy and side effects.

Methods: Patients with lumbar radicular symptoms for at least 6 months were randomized to equipotent doses of MPA 80 mg or DP 15 mg by lumbar translaminar epidurals administered under fluoroscopy. The epidurals were administered by different nonblinded practitioners other than the authors. Preprocedure Visual Analog Scale (VAS) pain scores by preoperative pain clinic nursing staff not involved in the study. On follow-up for the second epidural at 1 to 2 months, VAS scores and any reports of adverse side effects were obtained by pain clinic nursing staff who were blinded to the type of corticosteroid used. Electronic records were also reviewed for intervening changes in medication, additional therapeutic modalities, emergency room visits, and any other complications missed on nursing follow-up.

Results: There were no significant demographic differences between the DP group (N = 30) and MPA group (N = 30). The mean days to follow-up was less for the DP group (41.1) versus the MPA group (51.1), although the difference was not statistically significant ($P = 0.4284$). Comparing the DP group and MPA group, there was a smaller mean decrease in VAS for the DP group (−19.7%) versus the MPA group (−27.2%), although the difference was not statistically significant ($P = 0.3672$). Eighty-seven percent of patients in the MPA group and 90% in the DP group had decreases in postprocedure VAS with no statistically significant difference between the 2 groups ($P = 0.999$). Thirteen percent of the MPA group and 10% of the DP group had increases in postprocedure VAS with no significant difference between the 2 groups ($P = 0.999$). The percentage increase in postprocedure VAS for those who had increase in pain was 34.3% and 31.7% for the MPA and DP group, respectively with no statistically significant difference noted ($P = 0.8657$). Review of electronic medical records showed no change in pain medication prescribed, emergency room visits for pain, or any new treatments for pain in either group. No complications were reported by patients on nursing follow-up or seen in review of medical records including new neurological symptoms or new areas of pain.

Conclusions: Nonparticulate DP seems to be close to the safety and effectiveness of particulate MPA in the treatment of lumbar radiculopathy. There is, however, a statistically nonsignificant trend toward less pain relief and shorter duration of action that may be clarified in a larger and longer duration study.

Key Words: lumbar radiculopathy, glucocorticoids, corticosteroids, pain, dexamethasone, methylprednisolone, neurotoxicity, efficacy

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Lumbar epidural steroids injections have been a well reviewed controversial treatment for lumbar radiculopathy.[1–3] Particulate steroids such as methylprednisolone acetate (MPA) have been extensively used and studied.[4–17] Epidural nonparticulate corticosteroid dexamethasone phosphate (DP) has been used in only few small studies involving treatment for conditions such as cervicogenic headache, postoperative pain, and back pain after a labor epidural, and prevention of scar formation after laminectomy.[18–22] DP has the advantage of being more widely available and cheaper than MPA without polyethylene glycol (PEG), which have been shown to decrease compound action potentials of A, B, and C fibers.[23] Some commercially available preparations of MPA and DP may contain benzyl alcohol, which has also been associated with paraplegia.[24]

Only 1 paper by Pauza et al[25] used epidural DP for lumbar radiculopathy but this study was small with only 10 patients and involved low dose of DP of 8 mg in 72 hours delivered by a catheter. Recently the use of DP has been promoted in 1 retrospective study by Lee et al[26] and 1 small prospective study by Dreyfuss et al[27] as a safer corticosteroid for the treatment of cervical radiculopathy with cervical transforaminal injections. Both the studies compared DP versus another particulate corticosteroid triamcinalone. They used, however, different relative doses of triamcinalone and DP. The Dreyfuss et al[27] study was limited in a number of total study patients of 30 and was not randomized. No studies have compared the relative clinical effectiveness and neurotoxcity of equivalent doses of MPA versus DP in the treatment of lumbar radiculopathy through the translaminar epidural route. Soluble steroids such as DP have the theoretical disadvantage of washing out of the epidural space faster although DP has the longer half-life than MPA.[28] On the basis of current literature, we wanted to test the hypothesis that epidural nonparticulate corticosteroids such as DP are equally

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efficacious and at least equal in safety to particulate corticosteroids such as MPA.

METHODS

After institutional review board approval, patients were recruited for the study from new patients evaluated at Henry Ford Hospital Anesthesia Pain Service in Detroit Michigan from July 21, 2008 to July 21, 2009. The inclusion criteria for all patients were as follows: lumbar radicular symptoms below the knee that correspond to lumbar magnetic resonance imaging pathology, ≥ 18 years old, pain for at least 6 months, failed medication and physical therapy, no litigation, no history of psychopathology, Beck Depression Inventory < 15, no history of substance abuse, and no contraindication to intra-axial procedures. After informed consent was obtained, patients were randomized by a computer random number generator (0 = DP, 1 = MPA) to receive equipotent doses of epidural MPA (Pharmacia-Upjohn, Kalamazoo, MI) or DP (APP Pharmaceutical, Schaumburg, IL) at 80 mg and 15 mg, respectively[29–30] mixed with preservative free saline and 2 mL of 0.25% preservative free marcaine to a total volume of 10 mL. All patients had lumbar translaminar epidurals administered under fluoroscopic guidance with confirmatory epidurogram using 1 mL isovue m-300 at the level of pathology seen on magnetic resonance imaging. The procedures were performed by pain clinic staff physicians who were not involved in the study. They were not blinded to the type of corticosteroid mixed in the injection syringe, as the MPA and DP physically appear different in solution. Their procedure documentation, however, only recorded that "a corticosteroid solution was injected per study protocol". The type of corticosteroid used was kept in a secure password protected computer accessed only by the authors.

Preprocedure pain scores were obtained by pain clinic preoperative nursing staff not involved in the study using Visual Analog Scale (VAS) as per usual preprocedure nursing assessment. Patients as per clinic routine were scheduled for a second epidural within 1-2 months based on scheduling availability. On follow-up for the second epidural, VAS scores were obtained again by pain clinic preoperative nursing staff who were blinded to the type of corticosteroid used and the patients were interviewed for any adverse side effects such as new paresthesias, weakness, and new pain symptoms as per usual pain clinic routine. As Henry Ford Health System is a staff-model integrated health system with a unified electronic medical record system, all records were reviewed for intervening changes in medication, additional therapeutic modalities, emergency room visits, and as a check of any complications not reported on pain clinic nursing follow-up. Patient demographic information including age, sex, height, weight, body mass index (BMI), and preprocedure VAS was obtained. On follow-up for the second epidural postprocedure VAS and days to follow-up were recorded.

Comparisons were made between the MPA and DP study groups for the preprocedure demographic data. Percentage change in VAS, percentage of patients with decreased VAS, percentage of patients with increase VAS, days to follow-up, and reported complications were compared between the 2 study groups. Student *t* test was used to calculate *P* values for mean comparisons are made on the basis of age, height, weight, BMI, preprocedure VAS. Fisher exact test was used to calculate *P* values testing for proportional difference in sex. Nonparametric Kruskal-Wallis test was used to test for distribution differences between the 2 groups for preprocedure and postprocedure VAS and number of days to follow-up. The Student *t* test was used to calculate *P* values for mean comparisons are made on the basis of age, height, weight, BMI, percent change and percent change for those who saw an increase VAS scores. Fisher exact test was used to calculate *P* values testing for proportion differences between sex and the 2 treatment groups, and testing for proportion differences between those who saw increases or decreases of VAS scores, and the 2 treatment groups. The nonparametric Kruskal-Wallis test was used to test for distribution differences between treatment group samples for pre and post VAS scores. The distributions for these last 2 measures failed normality testing carried out to check whether assumption requirements were met to apply the more standard parametric tests, such as the Student *t* test.

TABLE 1. Demographics and Results

Factor	Response	Depomedrol (N = 30)	Dexamethasone (N = 30)	*P*
Age, N, mean (SD)		30, 63.7 (13.1)	30, 65.9 (13.5)	0.5255
Sex				
Female		24 (80%)	26 (87%)	0.7306[F]
Male		6 (20%)	4 (13%)	
Height, N, mean (SD)		30, 65.5 (3.0)	30, 64.4 (2.9)	0.1477
Weight, N, mean (SD)		30, 192.9 (44.7)	30, 198.0 (36.4)	0.6309
BMI, N, mean (SD)		30, 31.4 (6.2)	30, 33.7 (6.7)	0.1741
Pre VAS, N, mean (SD)		30, 77.3 (17.9)	30, 78.3 (18.8)	0.7998[KW]
Post VAS, N, mean (SD)		30, 54.2 (26.3)	30, 60.9 (20.2)	0.2917[KW]
Days to follow-up, N, mean (SD)		30, 51.1 (41.2)	30, 41.1 (18.1)	0.4284[KW]
Percent change of VAS, N, mean (SD)		30, −27.2 (36.8)	30, −19.7 (26.5)	0.3672
Percentage of patients with Increase/Decrease pain	Decrease	26 (87%)	27 (90%)	> 0.999[F]
	Increase	4 (13%)	3 (10%)	
Pain increased group percent change VAS, N, mean (SD)		4, 34.3 (21.1)	3, 31.7 (16.1)	0.8657

BMI indicates body mass index; F, Fischer exact test; KW, Kruskal-Wallis test; SD, standard deviation; VAS, visual analog scale.

RESULTS

Demographics

A total of 61 patients were recruited in the study with 31 receiving DP and 30 MPA. One DP patient was lost to follow-up and was not included in the study. For the DP group, the mean demographic data were as follows: age (65.1 y), sex (82% female, 17% male), height (64.4 inches), weight (198 lbs), BMI (33.7), and preprocedure VAS (78.3 mm) (Table 1). For the MPA group the average demographic results were as follows: age (63.7 y), sex (80% female, 20% male), height (65.5 inches), weight (192.9 lbs), BMI 31.4, and preprocedure VAS (77.3 mm) (Table 1). No statistically significant differences between the 2 groups for age ($P = 0.5255$), sex ($P = 0.7306$), height ($P = 0.1477$), weight ($P = 0.6309$), BMI ($P = 0.1741$), and preprocedure VAS ($P = 0.7998$) was noted (Table 1). The mean days to follow-up was lesser for the DP group (41.1) versus the MPA group (51.1), although the difference was not statistically significant ($P = 0.4284$) (Table 1).

Percentage Change in VAS and Complications

There was less mean decrease in VAS for the DP group (-19.7%) versus the MPA group (-27.2%), although the difference was not significant ($P = 0.3672$) (Table 1). Eighty-seven percent of patients in the MPA group and 90% in the DP group had decrease in postprocedure VAS with no statistically significant difference between the 2 groups ($P = 0.999$) (Table 1). Thirteen percent of the MPA group and 10% of the DP group had increase in postprocedure VAS with no statistically significant difference between the 2 groups ($P = 0.999$) (Table 1). The percentage increase in postprocedure VAS for those who had increase in pain was 34.3% and 31.7% for the MPA and DP group, respectively with no statistically significant difference noted ($P = 0.8657$) (Table 1). Review of electronic medical records showed no change in pain medication prescribed, emergency room visits for pain, or any new treatments for pain in either group. No complications were reported by patients including new neurological symptoms or new areas of pain. The 1 patient who did not complete follow-up received an inadvertent injection of the DP epidural solution intrathecally with subsequent spinal anesthesia recovered sensory and motor function in 4 hours and discharged home. Review of the electronic medical records on follow-up with the patient's primary physician at 1 and 2 months self-reported no long-term complications.

Power of Study

The study sample size of 30 per group gives 80% power to detect an effect size of 0.74 for a 2-sample t test. For the percent change in VAS, with a standard deviation of 32%, this means a difference of 24% would be detectable with 80% power. For follow-up days with a standard deviation of 31.8 days, a difference of 24 days would be detectable with 80% power.

DISCUSSION

Efficacy of MPA

The use of commercially available MPA injected into the epidural space as a treatment for lumbar radiculopathy has been evaluated in multiple studies with mixed results. There are several large (250 to 500 patients) and small (20 to 36 patients) retrospective studies showing a mix of acute and chronic benefit from epidural MPA (5, 6, 8, 9, and 10). Fewer prospective studies have been carried out without placebo control which showed some acute benefit.[12–14] A handful of randomized, placebo-controlled trials have been carried out that reinforced the short-term benefit of epidural MPA. Carrette et al[31] in 1997 carried out a randomized double-blind trial and compared 80 mg of methylprednisolone in 8 mL of saline compared with 1 mL of saline in 158 patients with sciatica due to lumbar herniated disc.[18] They reported short-term pain relief from leg pain at 6 weeks but afforded no improvement in function or need for surgery. Buchner et al[15] in 2000 carried out a randomized prospective clinical trial of 100 mg of MPA versus no steroid in 36 patients with lumbar radiculopathy due to prolapsed lumbar disc. Seventeen patients received MPA with marcaine in a series of 3 injections and VAS; they were assessed by a straight leg raise test and Hannover Functional Ability Questionnaire at 2 weeks, 6 weeks, and 6 months. Straight leg raise was better at 2 weeks with marginal improvement in pain and function. After 6 weeks no significant difference was noted between the 2 study group studies. One of the earliest studies of MPA by Snoek et al[4] in 1977 compared epidural MPA with saline in 51 patients with multiple diagnoses including lumbar degenerative disc disease and found no difference in the 2 study groups in a small prospective study. Several prospective, randomized, placebo-controlled studies have failed to show benefit, especially in the long-term.[7,11,16]

Efficacy of DP

Compared with MPA, DP has very limited number of studies looking at its efficacy and safety. Pauza et al[25] in 2005 performed a pilot study of 10 patients who received 8 mg of dexamethasone diluted in saline for a total volume of 72 mL in a continuous epidural infusion by a catheter at 1 mL/h for 72 hours for the treatment of lumbar radiculopathy. They reported no morbidity or mortality with mean VAS improvement of 46.7%. Most of the remaining studies involving epidural DP have been involved treatment for conditions other than lumbar radiculopathy. Dreyfuss et al[27] in 2006, prospectively compared pain relief in 30 patients who received single cervical transformational injection of triamcinolone or MPA for cervical radiculopathy at 4 weeks. They reported the effectiveness of MPA (12.5 mg) was slightly less than triamcinolone (60 mg) but was not statistically significant. This is consistent with our study results and the equipotent dosage ratios used are similar to those used in our study. This is in contrast with Lee et al[26] 2009 who retrospectively compared the particulate steroid triamcinolone (40 mg) with DP (10 mg) in cervical transformational epidural injections for the treatment of cervical radiculopathy in 159 nonrandomized patients. No complications were reported in either group and they reported no significant difference in the 2 groups at short-term follow-up of 4 to 31 days. The dose of DP relative to triamcinalone was lower than in our study and the earlier mentioned study by Dreyfuss et al.[27] Several small studies and case reports have reported use of epidural DP for reasons other than for the treatment of lumbar radicular pain such as backache after obstetric epidural, cervicogenic headache, and postoperative pain without any reports of clinical neurotoxicity.[18–21]

TABLE 2. Corticosteroid Brands and Preservative Content

Manufacturer	Polyethylene Glycol	Benzyl Alcohol
Methylprednisolone		
Upjohn-Pharmacia	+	−
Pfizer US Pharmaceuticals	+	+
Sandoz	+	−
Sicor Pharmaceuticals	+	+
Dexamethasone		
APP Pharmaceutical	−	+
Sicor Pharmaceutical	−	+
Baxter Anesthesia/Critical Care	−	+
American Reagent	−	−

Neurotoxicity, Side Effects, and Pharmacology

MPA has been well studied without significant neurotoxicity reported clinically. The evidence for clinical safety with epidural DP is limited to the few small studies mentioned earlier. Water soluble corticosteroids have been implicated in siezures in animal studies but no siezures were reported in our patients even in the 1 inadvertent intrathecal injection.[28,32,33] Animal studies for both MPA and DP have not showed any histologic evidence of neurotoxicity.[34–36] There is, however, evidence for neurotoxicity in the additives used in commercial preparations of corticosteroids such as PEG and benzyl alcohol.[27,28] Owing to concerns about these additives, it has been recommended that corticosteroid preparations should be diluted before epidural placement.[23] Most commercially available MPA contains PEG and benzyl alcohol (Table 2). Most commercially available DP does not contain PEG but does contain benzyl alcohol. American Regent, however, does produce DP without the PEG and benzyl alcohol although it does have parabens, which can increase the possibility of allergic reactions.[37] This study reconfirms the animal studies with no clinical neurotoxicity noted despite 1 intrathecal injection of DP. Information about side effects were, however, obtained both prospectively and retrospectively in this study and the small numbers in this study receiving DP does limit any definitive conclusions about the safety of routine use of epidural DP.

In terms of pharmacology, there are some potential differences in relative glucocorticoid and mineralocorticoid activity between the 2 drugs and differences in half-life and solubility that could affect clearance from the spinal canal. These differences may have implications for either benefits or harms. DP has a relative glucocorticoid activity of 25 to 80 times hydrocortisone versus MPA of 5 times hydrocortisone.[29,30] DP has no mineralocorticoid activity whereas MPA has 0.5 times relative activity compared with hydrocortisone.[29,30] A study by Maillefert et al[38] however, does cast doubt on the clinical significance of DP's greater glucocorticoid activity epidurally. The half-life of DP is longer at 36 to 54 hours versus MPA half-life of 18 to 40 hours.[29,30] The longer half-life of DP may be mitigated by the fact that the soluble steroids have the potential to be rapidly cleared from the spinal canal.[28] Particle size differences and aggregation differences have been seen with MPA having greater size particles and aggregations of MPA with dilution.[39,40] One may speculate that the larger size particles with dilution may prolong the ability of MPA to remain in the epidural space. The trend of the data in this study does point to the possible longer duration of action of MPA versus DP epidurally, but this study was limited in that the follow-up was less than 3 months.

CONCLUSIONS

Lumbar translaminar epidural injection using DP does appear effective in the short-term in the treatment of chronic lumbar radiculopathy without significant side effects. No clinical evidence of neurotoxicity was noted in this study. The partially retrospective nature of this study in terms of side effects and small numbers of patients who received epidural dexamethasone makes it difficult to say definitively that dexamethasone is safe for routine use in the epidural space. As a nonparticulate soluble corticosteroid, it is statistically equivalent in decreasing pain when compared with the more widely used particulate MPA. There does, however, seem to be some statistically nonsignificant trend toward DP being slightly less effective and of shorter duration than MPA. This trend may be further clarified by a larger study of longer duration.

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