Evaluation of Epidural Analgesic Paste Components in Lumbar Decompressive Surgery: A Randomized Double-Blind Controlled Trial

BACKGROUND: Adjuncts for pain management in lumbar decompressive surgery are needed to reduce narcotic consumption and promote early mobility.

OBJECTIVE: To evaluate the efficacy and active components of a previously described epidural analgesic paste in controlling postoperative pain and facilitating early discharge from hospital after lumbar decompressive surgery.

METHODS: A randomized double-blind controlled trial was conducted. Two-hundred and one patients were randomized to 1 of 4 analgesic epidural pastes at the time of lumbar spinal surgery: combination paste (morphine + methylprednisolone), steroid paste (methylprednisolone alone), morphine paste (morphine alone), or placebo. The primary outcome measures used were analgesic consumption and the McGill Pain Questionnaire (MPQ). Secondary outcome measures were: modified American Spinal Cord Injury Association (ASIA) score, Short Form 36 General Health Survey (SF-36), Aberdeen Pain Index (ABPI), time to ambulation and time to discharge from hospital.

RESULTS: Administration of combination and steroid paste, but not morphine paste, resulted in a statistically significant reduction in mean pain rating index (PRI) and present pain intensity (PPI) components of the MPQ in the first 3 days after surgery. Likewise, postoperative in-patient narcotic analgesic consumption was reduced in the combination paste and steroid paste group, but not in the morphine paste group. No difference in time to ambulation or discharge, SF-36 scores, ABPI scores, or neurologic recovery was observed.

CONCLUSION: An analgesic paste containing methylprednisolone acetate is effective at reducing postoperative pain after lumbar decompressive surgery. Mixing effective doses of morphine sulfate in the paste abrogates the expected analgesic effects of epidural morphine.

KEY WORDS: Analgesics, Discectomy, Laminectomy, Pain, Outcome
abdominal aortic aneurysm repair,\textsuperscript{4} thoracotomy,\textsuperscript{5} and total hip and knee replacements.\textsuperscript{5} However, the experience with epidural analgesics in lumbar decompressive surgery has been limited. Epidural administration of 3 mg morphine at the completion of laminectomy has been found to prolong the postoperative pain-free interval in 2 randomized controlled studies with 16 patients in 1 study and 17 patients in the other receiving morphine.\textsuperscript{7,8} However, the duration of analgesic effect was short-lived, at approximately 1 day, due to the rapid absorption of morphine in the epidural space. In an attempt to prolong pain control, Gibbons and colleagues\textsuperscript{9} retrospectively studied the use of absorbable gelatin sponges impregnated with 2 to 4 mg morphine and 40 to 80 mg methylprednisolone acetate in 45 patients. They found that it reduced the length of hospital stay and postoperative narcotic use. In addition, their patients reported improved pain control. The use of morphine in combination with methylprednisolone, aminocaproic acid, and microfibrillar collagen to create a paste-like mixture has been reported to successfully reduce postoperative pain when applied to the epidural space in patients undergoing elective lumbar decompressive procedures.\textsuperscript{10} A single randomized double-blind placebo-controlled trial has evaluated the efficacy of an epidural analgesic paste containing a mixture of morphine sulfate (Duramorph; Baxter Healthcare, Deerfield, Illinois) and methylprednisolone acetate, finding it to be effective at reducing postoperative narcotic consumption and self-reported pain scores.\textsuperscript{11}

The purpose of the present study was to confirm the efficacy of this analgesic paste when applied to the epidural space during lumbar spinal decompressive surgery. In addition, we sought to study the individual components of the paste to determine if they were most effective in isolation or in combination. Specifically we were interested in determining whether methylprednisolone acetate, morphine sulphate, or a combination of the 2 provided the most postoperative pain relief.

**METHODS**

**Patient Selection**

The research protocol for this study was approved by the Calgary Region Conjoint Health Research Ethics Board. Study subjects were accrued between September 1997 and September 2004. Adult patients undergoing elective lumbar microdiscectomy or laminectomy for spinal stenosis within the Division of Neurosurgery at the Foothills Medical Centre in Calgary, Alberta were identified at the time of initial (outpatient) consultation. Each patient underwent a process of informed written consent. Exclusion criteria included: planned fusion or instrumentation; surgery extending above L1; failed back syndrome; cerebrospinal fluid leak; conus injury; radiographic evidence of mechanical instability (including spondylolisthesis and scoliosis); known hypersensitivity to morphine or methylprednisolone; primary language other than English; and unavailability for extended follow-up. Prior decompressive surgery at the index level, adjacent levels, or in other locations was not an exclusion criterion.

**Randomization and Sample Size**

Patients were assigned to one of 4 groups on the day of surgery designed to test the paste with all active components (combination paste), methylprednisolone alone (steroid paste), morphine sulphate alone (morphine paste), or inactive placebo (placebo paste) (Table 1). Randomization was performed by a computer-generated table supplied by the Department of Epidemiology, University of Calgary. Patients were stratified according to procedure (laminectomy or microdiscectomy). Previously published data demonstrated outcome measures most sensitive to analgesia to be McGill pain scores and postoperative oral analgesic consumption.\textsuperscript{11} To detect a difference of 3.5 and 0.9 points in the McGill number of words chosen (NWC) and present pain intensity (PPI) scores respectively, and to detect a 20-mg difference in morphine consumption, 40 patients were required in each of the 4 treatment arms (alpha = 0.05, beta = 0.80). To allow for protocol violations and drop-out, study accrual was continued in all arms until each one had at least 50 patients.

**Surgical Protocol and Postoperative Analgesia**

All patients received a standard inhalational anesthetic with supplemental oxygen, nitrous oxide, and volatile anesthetic at the discretion of the attending anesthesiologist. Surgery consisted of either laminectomy for spinal stenosis or microdiscectomy for herniated lumbar disc, as determined by the preoperative diagnosis. All surgeries were performed at a single institution by the recruiting surgeon (RJH, MEM, TM, MGH, SD, GRS, ZK, WH, KMH) with open surgical technique. The paste was supplied to the operating room with its constituent components premixed in a total volume of 10 to 14 mL solution based on randomized group assignment (Table 1). Preparation of the paste was supervised by a pharmacist not directly involved in patient care on the day of surgery. The paste formulation differed from that reported by Needham,\textsuperscript{10} because the complete morphine dose was added to the paste initially rather than having a portion injected into the surrounding musculature following application. The estimated cost of the paste in its entirety was approximately $25 (US) based on individual component prices.

Methylprednisolone acetate injectable suspension (Depo-Medrol; Upjohn Company, Kalamazoo, Michigan) and Duramorph are approved by the US Food and Drug Administration for use in the epidural space; however, Avitene (Bristol Healthcare; Davol Inc., Cranston, Rhode Island) and Amicar (aminocaproic acid; Immunex Corp., Seattle, Washington) were used off-label. The combination product has not been subjected to the regulatory approval process. After ensuring hemostasis, the analgesic paste was applied to the epidural space such that the volume of paste was approximately the volume occupied by the removed lamina. After watertight closure of the lumbodorsal fascia, the subcutaneous tissue was irrigated thoroughly with fluid collection (CW Needham, personal communication, 1998). No intraoperative postcessional anti-inflammatory drug administration was permitted. Morphine 2 mg IV was administered for postoperative analgesia every 5 minutes as needed when requested by the patient. Vital signs were monitored postoperatively on a routine basis, and standard nursing care was provided including screening for urinary retention.

**Outcome Measures**

After enrollment into the study and prior to the day of surgery, patients underwent a detailed neurologic examination and completed 3 questionnaires: the McGill Pain Questionnaire (MPQ), the Aberdeen Back Pain Index (ABPI), and the Short Form 36 General Health Survey (SF-36). The MPQ, ABPI, and SF-36 questionnaires were readministered postoperatively on days 1, 3, and 7, and at weeks 3, 6, 12, 24, and 58. All 3
Three components of the MPQ were used:

1. Depo-medrol (2 cc) 80 mg
2. Aminocaproic acid: Amicar (2 cc) 500 mg
3. Preservative-free morphine sulphate: Epimorph (6 cc) 3 mg

These components were used to quantitatively assess the patient’s pain, including rank value pain rating index (PRI), NWIC, and PPI. The ABPI was used to estimate the influence of low-back and radicular symptoms on daily activities, while the SF-36 provided an index of overall general health perception.

Neurologic examination was performed preoperatively and 1 day, 8 weeks, and 1 year postoperatively to determine modified American Spinal Cord Injury Association (ASIA) scores, and root tension signs (straight leg raise). Narcotic and nonnarcotic analgesic administration was recorded preoperatively, as an inpatient, and as an outpatient at 1 week, 12 weeks, 24 weeks, and 58 weeks. The data for analgesic consumption were expressed as equivalent analgesic units in which 1 unit of codeine was equivalent to the effect of 60 mg of codeine. Patient vital signs, including maximum temperature, maximum and minimum blood pressures, and minimum oxygen saturation were recorded when available. The level of activity of postoperative patients was assessed by time to ambulation and time to discharge after surgery. Patients were screened in hospital and as outpatients for complications such as urinary retention, pruritus, infection, deep venous thrombosis, and recurrence of symptoms. Follow-up was undertaken over a 3-year period to observe for long-term complications such as epidural fibrosis or recurrent disc herniation with chronic pain and disability.

### Data Analysis

Questionnaires were scored by an on-site study nurse. All data were analyzed by an investigator (RD) not involved in the operative or postoperative care or in the collection of data. Descriptive statistics were compiled for all demographic, primary, and secondary outcome measures. Normal distribution of the data was verified using the Kolmogorov-Smirnov test with Lilliefors’ correction. Means from normally distributed data were analyzed by the Kruskal-Wallis H test, and multiple pair-wise comparisons were performed using the Mann-Whitney U test. Change in measures over time within and between groups was determined by repeated measures analysis with post-hoc least significant difference testing if a significant difference was found between groups. Examination of categorical data was performed by the chi square test. Probability levels for significance were defined as a value less than or equal to .05. Descriptive values presented here are expressed as mean ± standard error of the mean unless otherwise specified.

### RESULTS

A total of 224 randomization events occurred. In the discectomy group, surgery was canceled but rescheduled for 2 patients; the investigational agent was not used in 3 patients; and 11 patients withdrew after randomization. In the laminectomy group, surgery was canceled but rescheduled for 1 patient; the investigational agent was not used in 3 patients; and 3 patients withdrew after randomization. A total of 201 patients participated in the study (48 combination paste, 51 steroid paste, 50 morphine paste, and 52 placebo) and were stratified for operative procedure (101 discectomy and 100 laminectomy). Outcome measures up to 58 weeks are reported, as the rate of questionnaire completion fell below 70% after 1 year. Table 2 demonstrates the follow-up rates for primary and secondary outcome measures up to 1 year.

### Comparability Between Groups

All 4 groups were similar with respect to demographic characteristics (Table 3). There was no significant difference in the average patient age between groups ($F = 0.277, P = .842$) or...
the number of male and female patients between groups \((X^2 = 4.089, P = .252)\). More men \((n = 120)\) than women \((n = 81)\) were enrolled in the trial. There was no statistically significant difference in the number of comorbid conditions per patient \((F = 0.958, P = .414)\), preoperative McGill Pain Questionnaire scores \([\text{PRI} \times X^2 = 2.256, P = .521]\), \(\text{NWC} \times X^2 = 4.521, P = .210]\), SF-36 scores \((F = 1.521, P = .210)\), ABPI scores \((X^2 = 6.184, P = .103)\), and narcotic \((X^2 = 3.081, P = .379)\) and non-narcotic \((X^2 = 4.677, P = .197)\) analgesic use between the 4 treatment groups. Preoperative neurologic assessment also was similar between groups, with no statistical difference in sensory (light touch \(X^2 = 3.114, P = .374\); pinprick \(X^2 = 2.162, P = .540\)) and motor \((X^2 = 3.450, P = .327)\) ASIA scores and bilateral straight leg raising \((\text{right} X^2 = 3.165, P = .367; \text{left} X^2 = 0.107, P = .991)\).

### Treatment Complications

There were no intraoperative complications related to epidural analgesic paste placement at the time of surgery. One patient experienced a pressure sore on the nose which was attributed to patient positioning. Temporary postoperative urinary retention occurred in 19 patients \((4 \text{ combination}, 5 \text{ steroid}, 6 \text{ morphine}, 4 \text{ placebo})\) with no significant difference between groups \((X^2 = 0.65, P = .886)\). Pruritus occurred in one patient who received morphine paste and one who received steroid paste. Serous discharge from the incision occurred in one patient each from the placebo, combination, and steroid paste groups. Incisional erythema was observed in one placebo and 2 steroid paste patients. Only one wound infection was observed, occurring in a patient who received steroid paste.

### Hospital Course

Patients were closely monitored for alterations in oxygen saturation, temperature, and blood pressure during their hospital stay. Mean body temperature for patients receiving combination paste \((37.7 \pm 0.1^\circ\text{C})\) and steroid paste \((37.6 \pm 0.1^\circ\text{C})\) was lower than that for patients who received the morphine paste \((38.2 \pm 0.1^\circ\text{C})\) and placebo paste \((38.2 \pm 0.1^\circ\text{C})\). This difference was statistically significant \((F= 10.697, P < .001)\). No statistically significant difference in mean maximum systolic \((F = 0.471, P = .703)\), mean maximum diastolic \((F = 0.993, P = .398)\), mean minimum systolic \((F = 0.703, P = .552)\), or mean minimum diastolic blood pressures \((F = 0.154, P = .927)\) was observed. There was also no difference between groups in the mean minimal oxygen saturation recorded during the in-patient period \((F = 1.299, P = .280)\).

### Primary Outcome Measures

Within the first 7 days after surgery, PRI and PPI components of the McGill Pain score differed significantly between treatment groups \((\text{repeated measures ANOVA; PRI } P = .042; \text{ PPI } P = .019)\) (Figure 1). A similar trend was seen in the NWC component but did not reach statistical significance \((P = .081)\). Post-hoc analyses revealed a significant reduction in mean PPI scores for patients receiving the combination paste compared to both the placebo \((P = .041)\) and morphine paste \((P = .026)\) groups. In addition, those who received steroid paste had significantly less pain compared with those who received morphine paste \((P = .016)\) and placebo paste \((P = .025)\). There was a similar significant reduction in mean PRI scores for patients receiving the combination paste compared with placebo \((P = .048)\). Mean PRI, PPI, and NWC scores decreased over time in all groups in a statistically significant manner \((P < .001 \text{ for all 3 measures})\), indicating a beneficial effect from surgical intervention.

Mean postoperative in-patient narcotic analgesic consumption was more than 3 times higher in the placebo group \((27.1 \pm 11.8 \text{ unit doses})\) compared with the steroid paste group \((8.4 \pm 1.1 \text{ unit doses})\) and more than 2 times higher compared with the combination paste group \((10.8 \pm 2.0 \text{ unit doses})\) (Figure 2). Narcotic analgesic consumption was significantly reduced during the postoperative in-patient period for patients in the steroid paste \((P = .001)\) and combination paste \((P = .003)\) groups compared with placebo. Similarly, during the same period, nonnarcotic analgesic use in the combination \((0.87 \pm 0.31 \text{ unit doses})\) and steroid paste groups \((0.29 \pm 0.11 \text{ unit doses})\) was

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### TABLE 2. Follow-up Percentages for Outcome Measures at Defined Time Points

|                      | Combination Paste | Steroid Paste | Morphine Paste | Placebo Paste |
|----------------------|-------------------|---------------|----------------|--------------|
| **McGill Pain**      |                   |               |                |              |
| Questionnaire        |                   |               |                |              |
| 1 day                | 100               | 98            | 100            | 98           |
| 3 days               | 98                | 98            | 98             | 96           |
| 7 days               | 98                | 96            | 98             | 96           |
| 3 weeks              | 100               | 98            | 98             | 96           |
| 6 weeks              | 98                | 100           | 100            | 96           |
| 12 weeks             | 100               | 98            | 98             | 94           |
| 6 months             | 98                | 94            | 96             | 92           |
| 1 year               | 88                | 84            | 92             | 85           |
| **Aberdeen Back**    |                   |               |                |              |
| Pain Index           |                   |               |                |              |
| 3 weeks              | 100               | 100           | 98             | 96           |
| 6 weeks              | 98                | 100           | 100            | 96           |
| 12 weeks             | 100               | 98            | 98             | 98           |
| 6 months             | 100               | 94            | 96             | 98           |
| 1 year               | 92                | 90            | 96             | 87           |
| **SF-36**            |                   |               |                |              |
| 3 weeks              | 100               | 96            | 100            | 98           |
| 6 weeks              | 96                | 100           | 100            | 96           |
| 12 weeks             | 98                | 98            | 98             | 94           |
| 6 months             | 96                | 94            | 96             | 90           |
| 1 year               | 85                | 82            | 92             | 85           |
| **ASIA**             |                   |               |                |              |
| 1 day                | 85                | 84            | 74             | 81           |
| 8 weeks              | 98                | 90            | 92             | 87           |
| 1 year               | 83                | 78            | 86             | 87           |
lower compared with the morphine (1.05 ± 0.29 unit doses) and placebo paste groups (1.50 ± 0.40 unit doses). This difference approached statistical significance (P = .057, Kruskal-Wallis). Nonnarcotic analgesic consumption was significantly lower at 1 week after surgery in the steroid paste group (1.54 ± 0.49 unit doses) compared with the placebo group (5.04 ± 1.36 unit doses) (P = .003, Mann-Whitney rank sum). The morphine paste group did not show a significant difference in narcotic or nonnarcotic analgesic use when compared with placebo during the postoperative in-patient period (8.55 ± 1.34 vs 7.26 ± 1.06 unit-doses, P = .888; 1.05 ± 0.29 vs 1.50 ± 0.40, P = .359, respectively). There was no difference in the cumulative narcotic consumption between groups at 1 week postoperatively (P = .21).

**Secondary Outcome Measures**

Neurologic examination revealed no statistically significant difference in modified ASIA motor scores, sensory scores, or straight-leg raise scores between groups postoperatively after 1 day, 8 weeks, and 1 year (Figure 3). Surgical intervention resulted in significant improvement in mean sensory score (P = .009) and mean left (P < .001) and right (P < .001) straight leg raise at 1 year in all groups. Motor scores remained unchanged compared

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**TABLE 3. Characteristics of the Study Population**

|                      | Combination Paste | Steroid Paste | Morphine Paste | Placebo |
|----------------------|-------------------|---------------|----------------|---------|
| Total No. Patients   | 48                | 51            | 50             | 52      |
| Female (%)           | 19 (40)           | 15 (29)       | 24 (48)        | 23 (44) |
| Male (%)             | 29 (60)           | 36 (71)       | 26 (52)        | 29 (56) |
| Average age (y)      | 51                | 52            | 54             | 52      |
| Smoking              |                   |               |                |         |
| Yes (%)              | 15 (31)           | 10 (20)       | 18 (37)        | 11 (22) |
| No (%)               | 33 (69)           | 40 (80)       | 31 (63)        | 40 (78) |
| Mean number of morbidities per patient (range) | 0.49 (0-4) | 0.65 (0-3) | 0.62 (0-4) | 0.42 (0-2) |
| Previous lumbar surgery | 4                | 2             | 4              | 3       |
| Duration of symptoms |                   |               |                |         |
| >1 year              | 21                | 18            | 16             | 21      |
| 6 months - 1 year    | 13                | 19            | 18             | 19      |
| 3-6 months           | 7                 | 11            | 11             | 5       |
| 6-12 weeks           | 6                 | 0             | 4              | 3       |
| <6 weeks             | 0                 | 1             | 0              | 1       |
| Location of maximal pain |          |               |                |         |
| Leg > back           | 30                | 30            | 31             | 28      |
| Back > leg           | 9                 | 11            | 12             | 7       |
| Leg = back           | 8                 | 6             | 6              | 14      |
to baseline at 1 year in all groups ($F = 2.230$, $P = .101$). The average time to ambulation for each group was: 6 ± 1 hours (combination paste), 8 ± 1 hours (steroid paste), 9 ± 1 hours (morphine paste), and 8 ± 1 hours (placebo paste). The average time to discharge for each group was: 41 ± 6 hours (combination paste), 58 ± 3 hours (steroid paste), 72 ± 5 hours (morphine paste), and 72 ± 6 hours (placebo paste). No statistically significant difference in time to ambulation ($F = 1.914$, $P = .131$) or time to discharge ($F = 2.231$, $P = .087$) was observed between groups.

General health perception was similar for all treatment groups at each of the time points up to 58 weeks ($P = .527$) (Figure 4). Similarly, there was no statistically significant difference in ABPI scores between the groups ($P = .884$; Figure 4). General health perception was similar for all treatment groups at each of the time points up to 58 weeks ($P = .527$) (Figure 4).
perception improved \((F = 117.564, P < .001)\), and ABPI scores decreased \((F = 98.234, P < .001)\) over 58 weeks after surgery. A statistically significant difference in general health perception was present postoperatively at 3 weeks in all groups (combination: \(t = 3.0061, df = 94, P = .003\); steroid: \(t = 2.1932, df = 98, P = .031\); morphine: \(t = 4.3621, df = 97, P < .001\); placebo: \(t = 4.0952, df = 99, P < .001\)). ABPI scores were significantly decreased postoperatively by 3 weeks in all groups (combo: \(t = 4.6623, df = 76, P < .001\); steroid: \(t = 3.2371, df = 70, P = .002\); morphine: \(t = 5.4904, df = 84, P < .001\); placebo: \(t = 4.8412, df = 78, P < .001\)).

**DISCUSSION**

Postoperative pain after lumbar decompressive surgery arises from multiple sources, including the inflammatory cascade triggered by tissue trauma, direct manipulation of lumbar nerve roots, and nociceptive input from manipulation of skin and muscle. The analgesic epidural paste described in this paper was designed to act locally on both neural elements and traumatized tissue beneath the lumbodorsal fascia. The paste in its original form has been shown to improve pain control in the immediate postoperative period and up to 6 weeks after surgery. In addition, epidural morphine and steroids have individually been shown to reduce pain after lumbar decompressive surgery. It is hypothesized that the morphine component has an analgesic effect by entering the CSF to act directly at the spinal cord level, inhibiting nociceptive input at the dorsal horns. While methylprednisolone is hypothesized to suppress mediators of pain and inflammation such as prostaglandins, leukotrienes, bradykinin, and histamine, recent studies also have highlighted potential central

![FIGURE 4. The analgesic paste did not adversely affect ASIA motor (A) and sensory (B) scores or straight leg raise angle (C, D) after lumbar decompressive surgery. Blue, combination; red, steroid; green, morphine; purple, placebo. ASIA, American Spinal Cord Injury Association; SEM, standard error of the mean.](https://example.com/figure4.png)
Our results indicate that methylprednisolone is a key ingredient producing the potent analgesic effect of the epidural paste, and that 3 or 5 mg of morphine administered in the described paste formulation is ineffective at producing the expected analgesic effects of morphine.

The efficacy of epidural morphine (1-5 mg) in pain relief after lumbar decompressive surgery has been previously confirmed by multiple studies.9,18,19,25-27 Specific factors such as unknown drug release time, tissue absorption, and small area of dural contact may have contributed to lack of demonstrated efficacy of epidural morphine administered in the paste formulation used in this study. The amount of epidural morphine used was fixed for every patient; it was not adjusted to prior narcotic exposure or in relation to patient age. Dose response studies have demonstrated significant analgesic effects of epidural morphine with doses greater than 3 mg.28,29 In a study that observed extended analgesia after lumbar microdiscectomy, epidural morphine contained in a gelatin sponge was administered at a dose determined by surgeon preference, taking into account patient size, history of narcotic use, and coping skills.3 The investigators used doses ranging from 2 to 4 mg. It is quite possible that 3 to 5 mg of epidural morphine in a paste formulation does not meet the overall threshold effect for analgesia in a patient population with varied narcotic exposure. Interactions of morphine with the other components of the paste may have affected release and distribution. Mastronardi et al27 found a reduction in visual analogue pain intensity and analgesic consumption when 1 mg of epidural morphine was administered in an Adcon-L (Gliltech Medical, Inc., Cleveland, Ohio) compound during lumbar microdiscectomy. The results of our experiment should not be interpreted to signify that morphine has no analgesic effect in the epidural space. In fact, the CSF penetration of epidural morphine30-32 and sites of action at the mu-opioid receptors of the spinal cord dorsal horns have been extensively documented. We hypothesize that the bioavailability of morphine was reduced and extended due to containment within a viscous compound. Higher morphine dosing within the paste might be expected to provide adequate morphine-related analgesia, and could be the focus of future investigations.

The lack of effect from morphine in this study suggests that the determinant of the analgesic effect of combination paste is primarily due to methylprednisolone. Indeed, although not statistically significant, patients who received methylprednisolone paste tended to have lower pain scores and reduced analgesic requirements, even compared with patients receiving the combination paste (Figures 1 and 2). Although higher doses of epidural morphine might further enhance the analgesic effect, such doses could precipitate undesirable side effects such as nausea and vomiting, pruritus, respiratory depression, and urinary retention.33,34 In this way, it is encouraging that methylprednisolone alone can be used with at least the same efficacy as the combination paste. This effect is hypothesized to arise from both anti-inflammatory and direct peripheral and central analgesic mechanisms.

The analgesic properties of corticosteroids have been detailed previously in application to lumbar nerve roots.19,35-37 In addition, there is a growing appreciation of analgesic effects mediated by steroids in the central and peripheral nervous systems.22,24,38-41 The use of steroid paste also may have secondary beneficial effects by limiting the degree of scar formation after lumbar surgery. Epidural scar is reduced following laminectomy in rabbits when triamcinolone is applied to the dura.42 Talc-induced arachnoiditis is reduced in rabbits35 and cat44 when intrathecal hydrocortisone is administered. In the present study, a reduction in post-surgical inflammation is suggested by the significantly lower mean body temperature observed in patients who received epidural steroids (combination and steroid paste) compared with those who did not receive the morphine or control paste. We did not have the opportunity to examine whether this equated to a reduction in postoperative scar tissue due to the confines of our protocol; however, this hypothesis is worthy of further investigation.

New drug effects, altered drug pharmacokinetics, and changed potency are possible for both methylprednisolone and morphine when considering the potential interactions in a 3- or 4-component paste. Therefore, comparison of the application of methylprednisolone in paste formulation vs direct epidural or even systemic steroid administration is warranted and might give the surgeon greater direction as to the optimal method of methylprednisolone administration for analgesic purposes. Careful evaluation of factors that may modify steroid analgesic effects, such as use of preoperative nonsteroidal anti-inflammatory drugs or long-acting morphine, would be essential to such a study.

The administration of lumbar epidural analgesic paste containing morphine or morphine combined with methylprednisolone did not result in an increased risk of postoperative urinary retention. The post-surgical risk of infection was 1 in 99 patients treated with analgesic paste containing methylprednisolone, and the overall risk of infection for the study population was 1 in 201. Due to the low rate of infection in the study population, the present study is underpowered to demonstrate a significant difference in infection rates between treatment groups. No adverse systemic effect on blood pressure was found in patients receiving methylprednisolone-containing paste. As expected, we did not observe differences among patients in the placebo, combination, morphine, or steroid paste groups with respect to quality-of-life measures (eg, ABPI scores and SF-36 scores) in the immediate or prolonged postoperative period. These instruments measure global outcomes over prolonged time periods and are unlikely to be sensitive to short-term discrete pain differences. These findings are in keeping with prior observations.11

Pre- and postoperative variables that were not under the direct control of the investigators were mitigated by utilizing a randomized, blinded, controlled trial design. The comparable nature of patients in the treatment and control groups is highlighted by similar baseline demographic profiles, clinical findings, and preoperative pain scores and analgesic consumption. Therefore, we are confident that our randomization allowed the balance of external factors that could have biased our observations. We were able to recruit sufficient patients into the study to achieve the
predetermined sample size. The internal validity of our observations is supported by the use of previously validated measures, internal consistencies within and between outcome measures, as well as theoretically expected analgesic effects of active compounds. Internal validity is also supported by the overall improvements in the MPQ, ABPI, SF-36, and neurologic examination results over time after surgical intervention over a 1-year period. Such improvement is expected in the normal postoperative course after lumbar decompressive surgery. The finding of this improvement lends credibility to the difference between groups that is demonstrated here using the same measurement tools. The consistent analgesic effect as quantified by reduction in both MPQ scores and analgesic requirements is further evidence of validity.

CONCLUSION

The results of this study demonstrate that application of an analgesic paste containing methylprednisolone to the exposed dura after lumbar decompressive surgery reduces the need for postoperative narcotic and non-narcotic analgesia, and provides superior pain control compared with current standard medical practice. The beneficial effects of the steroid or combination analgesic paste are present within 24 hours of application and persist for up to 7 days, consistent with the known CSF pharmacokinetics of methylprednisolone. In our hands the analgesic paste was safely administered with no adverse events attributable to the use of this compound. Administration of morphine in the epidural paste formulation abrogates the expected analgesic effect of morphine. We recommend that analgesic paste containing methylprednisolone be considered for pain control in patients undergoing routine lumbar decompressive surgery.

Disclosure

No external sources of funding were utilized in this study. Data acquisition and collation were carried out by a full-time research administrator paid through the University of Calgary Spine Program. The investigators did not receive renumeration outside of the usual surgical fees paid by Alberta Health and Wellness. The authors have no personal or institutional interest in any of the drugs, materials or devices described in this article.

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44. Feldman S, Behar AJ. Effect of intrathecal hydrocortisone on advanced adhesive bril- larrow collagen? To reproduce the excellent results presented in this paper, others would need to use a duplicate of the mixture from the Depo-Medrol paste group. A comparison of Depo-Medrol with and without the binder is another study. The effect on postoperative pain response of the Depo-Medrol paste may be altered by preoperatively given oral long-acting narcotics such as OxyContin, epidural narcotics delivered at the L3/L4 area via intraoperative catheter or separate needle injection, or a Fentanyl patch placed near the end of surgery. Other modalities of proactive pain management treatments such as nonsteroidal anti-inflammatory drugs, anticonvulsant drugs used for neuropathic pain, antidepressants, anti-emetics, and other drugs preoperatively or postoperatively remain to be investigated in future studies. There also can be subgroups within spinal surgery that respond more to Depo-Medrol than others for pain relief. This study involved a group of patients undergoing lumbar decompression who would have had a major component of radiculitis, and I surmise that the Depo-Medrol was active in this component of the pain. Thus, the pain relief results of this study may not be appropriate to extrapolate to fusion patients with mechanical pain. Additionally, steroids may interfere with the bony healing of the fusion in this group.

These questions do not represent problems with this excellent study, but rather a call for more research in postoperative pain management research and safely maximizing the proactive approach to pain treatment to make the surgical experience the easiest for the spectrum of patients receiving spinal surgery. Postoperative spinal surgery pain should not be considered an insolvable problem to be delegated to others, but rather an integral portion of the total operative experience to be studied and improved, like all the other aspects of spinal surgery.

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**COMMENTS**

The authors are to be congratulated on the completion of this landmark study in postoperative pain management after lumbar decompressive surgery. Although randomized studies are considered the gold standard, they are, unfortunately, rare. These authors not only have completed a randomized study but also have a study design and follow-up rate that will serve as an example for others in the future. This study, furthermore, was accomplished without a corporate sponsor, demonstrating what is possible without industry funding.

The authors have clarified the often quoted work of Needham in 1996 with the use of “morphine nerve paste” to control postoperative pain. By dividing the mixture into its components, the authors have definitively shown that the active ingredient is Depo-Medrol and not the morphine when these 2 drugs are mixed in a binder of aminocaproic acid and microfibrillar collagen and placed at the operative decompression site. It is notable that this study also follows a proactive rather than reactive plan of postoperative pain management. Although this study answers an important question and advances the field of postoperative pain management, other questions arise from the results. Does Depo-Medrol work as effectively (or more effectively?) without the binder of aminocaproic acid and microfibrillar collagen? To reproduce the excellent results presented in this paper, others would need to use a duplicate of the mixture from the Depo-Medrol paste group. A comparison of Depo-Medrol with and without the binder is another study.

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**Acknowledgments**

We thank all neurosurgical staff past and present at Foothills Medical Centre who participated in this trial through patient enrollment and surgical application of the study paste. Data management support for this study was provided by Ish Baines, MSc, and Yvette Andrews, RN. Clerical support provided by Patti Sullivan.

**EPIDURAL ANALGESIC PASTE IN LUMBAR DECOMPRESSIVE SURGERY**

**Comments**

The authors are to be congratulated on the completion of this landmark study in postoperative pain management after lumbar decompressive surgery. Although randomized studies are considered the gold standard, they are, unfortunately, rare. These authors not only have completed a randomized study but also have a study design and follow-up rate that will serve as an example for others in the future. This study, furthermore, was accomplished without a corporate sponsor, demonstrating what is possible without industry funding.

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short-term pain and narcotic use was improved with epidural paste containing methylprednisolone, time to discharge, cost-effectiveness, and long-term benefits have not been clearly demonstrated. The groups with steroids (which had the favorable outcomes) appear to have fewer comorbidity conditions than the placebo or morphine-alone groups, raising the question whether that difference accounts for any portion of the difference in outcome. In addition, the question of potential increase in wound complications, particularly infection, requires further study. It is understood that high-dose intravenous methylprednisolone may be a risk factor for systemic infection in patients with acute spinal cord injury, and it may prove to carry a similar risk with epidural application.1 In this study, the single wound infection happened to be in a patient receiving steroid paste. Although this may not be statistically significant, the issue will need to be assessed in future studies. Interestingly, in a previous study by the senior author using a combination (methylprednisolone and morphine) analgesic paste in a similar population of patients undergoing lumbar decompression surgery, the treatment group included 3 patients (out of 30) who had a wound complication (2 with superficial infections and 1 with serous drainage requiring additional suture), whereas the control group did not have any reported wound complications.2 In terms of efficacy, that study also showed benefit for postoperative pain and narcotic usage.

Overall, the authors are to be commended for their meaningful contribution that adds important evidence that epidural analgesic paste application can prove beneficial with lumbar decompressive surgery and that the steroid component appears to be the key component. Long-term follow-up of these patients, who were treated between 1997 and 2004, would be interesting to help determine if there are any long-term benefits, possibly related to reduced scar tissue development, as the authors postulate. Finally, additional (and larger) studies will be helpful to better determine the cost-effectiveness and safety of the perioperative analgesic paste use.

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1. Sayer FT, Kronwall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. Spine Jour. 2006;6(3):335-343.
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In this well-designed prospective clinical trial, Diaz et al. have evaluated the efficacy and active components of epidural analgesic paste for controlling postoperative pain after lumbar decompressive surgery. In this study, 201 patients were randomized to 4 different groups that included morphine plus methylprednisolone, methylprednisolone alone, morphine paste alone and placebo. The authors demonstrated that the administration of a steroid paste, but not morphine paste, was effective in controlling postoperative pain. The authors were able to successfully perform this important randomized clinical investigation with excellent patient follow-up as well as without corporate sponsorship. Other researchers should further investigate the use of analgesic paste containing methylprednisolone in reducing postoperative pain after lumbar fusion surgeries. The take-home message from the study is that the steroid component appears to be the key component to epidural analgesic paste. This randomized clinical investigation should serve as a benchmark for future spine investigations of other important clinical questions.

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