Epidural dexamethasone reduces postoperative pain and analgesic requirements

[L'administration péridurale de dexaméthasone réduit la douleur et la demande d'analgésiques postopératoires]

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Purpose: Epidural steroids may have potential advantages for providing postoperative analgesia. We therefore undertook a study to evaluate the efficacy of epidurally administered dexamethasone in reducing postoperative morphine requirements, as a measure of analgesia following laparoscopic cholecystectomy.

Methods: In a randomized, double-blind study, 94 patients undergoing laparoscopic cholecystectomy were randomly assigned to one of three groups. Group 1 (Control) patients received dexamethasone 5 mg iv with epidural injection of 0.25% bupivacaine 8 mL and normal saline 2 mL, Group 2 (D1) patients received normal saline 2 mL iv with epidural injection of 0.25% bupivacaine 8 mL and dexamethasone 5 mg in normal saline 2 mL, and Group 3 (D2) patients received normal saline 2 mL iv with epidural injection of dexamethasone 5 mg in normal saline 10 mL. After surgery, morphine 2–4 mg iv was administered as needed for analgesia. Postoperative morphine requirements, visual analogue scale (VAS) pain scores at rest and with effort, and time to first analgesic administration were recorded by a blinded observer.

Results: Total morphine consumption for the first 24 hr following surgery was lower in both epidural dexamethasone groups (D1, D2) compared to the control group ($P < 0.05$). The percentage reduction in morphine consumption in Group D1 was 53.9% and in Group D2 was 52.9% in the first 24 hr. Postoperatively at 12 hr, 18 hr and 24 hr, the VAS scores at rest and during effort were also lower in the epidural dexamethasone groups (D1, D2) compared to the control group ($P < 0.05$). The percentage reductions in VAS scores with effort at 12 hr, 18 hr and 24 hr in Group D1 were 50%, 52.9% and 50% respectively, and in Group D2 percentage reductions in pain scores with effort were 54.8%, 58.8% and 55.5% at corresponding sampling intervals.

Conclusion: Preoperative epidural administration of dexamethasone 5 mg, with or without bupivacaine, reduces postop-

erative pain and morphine consumption following laparoscopic cholecystectomy.

Objectif : Les stéroïdes périduraux peuvent avoir des avantages pour l'analgésie postopératoire. Nous avons donc entrepris une étude pour évaluer l'efficacité de l'administration péridurale de dexaméthasone dans la réduction des besoins postopératoires de morphine comme mesure de l'analgésie à la suite d'une cholécystectomie laparoscopique.

Méthode : Dans une étude randomisée et à double insu, 94 patients devant subir une cholécystectomie laparoscopique ont été répartis au hasard en trois groupes. Les patients ont reçu, dans le groupe 1, (témoin) 5 mg de dexaméthasone iv et l'injection péridurale de 8 mL de bupivacaine à 0,25 % et 2 mL de solution salée ; dans le groupe 2 (D1), 2 mL de solution salée iv et l'injection péridurale de 8 mL de bupivacaine à 0,25 % et 5 mg de dexaméthasone dans 2 mL de solution salée ; dans le groupe 3 (D2), 2 mL de solution salée iv et l'injection péridurale de 5 mg de dexaméthasone dans 10 mL de solution salée. Après l'opération, 2 – 4 mg de morphine iv ont été administrés au besoin pour l'analgésie. La demande de morphine postopératoire, les scores de douleur à l'échelle visuelle analogique (EVA) au repos et à l'effort et le temps précédant la première demande d'analgésie ont été enregistrés par un observateur objectif.

Résultats : La consommation totale de morphine pendant les 24 premières heures postopératoires a été plus faible dans les groupes D1 et D2, que dans le groupe témoin ($P < 0,05$). Pendant ces 24 h, le pourcentage de réduction de consommation de morphine a été de 53,9 % dans le groupe D1 et de 52,9 % dans le groupe D2. Les scores de l'EVA au repos et à l'effort, 12 h, 18 h et 24 h après l'opération, étaient aussi plus bas chez les patients des deux groupes D1 et D2 comparés aux témoins ($P < 0,05$). Le pourcentage des réductions des scores de douleur à l'effort à 12 h, 18 h et

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24 h ont été respectivement de 50 %, 52,9 % et 50 % dans le groupe D1 et de 54,8 %, 58,8 % et 55,5 % dans le groupe D2.

Conclusion : L'administration préopératoire de 5 mg de dexaméthasone, avec ou sans bupivacaine, réduit la douleur postopératoire et la consommation de morphine à la suite d'une cholécystectomie laparoscopique.

BENEFITS of laparoscopic cholecystectomy as compared to open cholecystectomy are well-established, and include shorter hospitalization, earlier return to work, better hospital bed utilization, and reduced costs.¹ Despite these benefits, postoperative pain remains the dominant complaint after laparoscopic cholecystectomy, and has great potential to be influenced by the anesthesiologist.²

The common analgesic modalities after laparoscopic cholecystectomy include non-steroidal anti-inflammatory drugs, wound infiltration with local anesthetics, and intraperitoneal administration of local anesthetics or saline, producing short-term benefits that do not necessarily translate into earlier discharge or improved postoperative function.³ Opioids provide good pain control in the postoperative period, but are associated with nausea and vomiting, sedation, pruritus and respiratory depression. As no single drug has been identified which specifically inhibits nociception without side effects, multimodal analgesic strategies are most commonly employed for postoperative analgesia. Trials evaluating multimodal analgesia in laparoscopic cholecystectomy suggest that clinically relevant benefits can be achieved.³ Thoracic epidural analgesia with morphine-bupivacaine combination improves pain relief during the first 24 hr following laparoscopic cholecystectomy.⁴

Preoperative administration of dexamethasone has been reported to reduce postoperative pain through both oral^{5,6} and *iv*^{7,8} routes of administration. While epidural steroids are effective in the treatment of low back pain,⁹ their potential postoperative analgesic benefits have not been evaluated. The safety of epidural steroid injections has been demonstrated.^{10,11} Although arachnoiditis has been reported in association with accidental intrathecal injection of depo-steroids^{12,13} this risk is considered to be minimal with dexamethasone as a result of its water-solubility.

Acute nociception at peripheral tissues leads to intraspinal prostaglandin synthesis by induction of cyclo-oxygenase-2 and activation of phospholipase A2, resulting in a hyperalgesic state.^{14,15} Corticosteroids

are known to inhibit phospholipase A2 and expression of cyclo-oxygenase-2 during inflammation, thus reducing prostaglandin synthesis.¹⁶ Intrathecal injection of corticosteroids in the rat model has been shown to have no effect on acute high intensity stimuli, despite a mild effect on nociceptor driven spinal sensitization.¹⁴

With this background knowledge, a randomized, double-blind study was undertaken to test whether a reduction in postoperative pain and morphine consumption could be achieved by preoperative administration of epidural dexamethasone, in patients undergoing laparoscopic cholecystectomy.

Methods

After approval from local Ethics Committee and obtaining written informed consent, 94 patients of either sex undergoing laparoscopic cholecystectomy were enrolled in this prospective, randomized, double-blinded study. Included were ASA class I and II patients, between 30–60 yr of age and weighing between 50–75 kg. Patients were excluded if they had any history of cardiac, respiratory, neuromuscular, hepatic or major renal disease. Patients were also excluded if they were obese, diabetic, or if they were receiving analgesics, corticosteroids or calcium channel blocking drugs. Finally, any contraindication to corticosteroids, or failure of the patient to understand the study procedure, resulted in their exclusion.

The study protocol, the epidural procedure, and the visual analogue scale (VAS) for pain were explained to each patient during the preoperative visit. Patient randomization was established with the use of computer-generated codes. Only the pharmacist and the statistician knew the identity of the study medication. Procedures were established to break the codes in the event of any adverse reaction. Group 1 (Control) patients received dexamethasone 5 mg *iv* with epidural injection of 0.25% bupivacaine 8 mL and normal saline 2 mL, Group 2 (D1) patients received normal saline 2 mL *iv* with epidural injection of 0.25% bupivacaine 8 mL and dexamethasone 5 mg in normal saline 2 mL, and Group 3 (D2) patients received normal saline 2 mL *iv* with epidural injection of dexamethasone 5 mg in normal saline 10 mL. The dexamethasone formulation was Decdan 4 mg·mL⁻¹ (Merind, Mumbai, India) with methyl- and propyl paraben preservatives. The final concentration for each group was established by mixing with the appropriate volume of normal saline.

On the day of surgery, patients were premedicated with midazolam 7.5 mg *po* 60 min preoperatively. In the operating room routine monitors were applied (electrocardiogram, non-invasive blood pressure mon-

itor and pulse oximeter). Patients were awake during thoracic epidural insertion. With the patient sitting and under aseptic conditions, the skin was infiltrated with 1% lidocaine 3 mL prior to insertion of an 18G Tuohy needle at the T₇₋₈ interspace. Upon establishing loss of resistance to air, a test dose of 2% lidocaine 3 mL with adrenaline 1:200000 was injected after negative aspiration. Five minutes later, patients were randomly allocated to receive a single-shot epidural injection and simultaneous *iv* injection according to group assignment.

Anesthesia was induced with propofol 2 mg·kg⁻¹ *iv* and fentanyl 2 µg·kg⁻¹ *iv*, with endotracheal intubation facilitated by vecuronium 0.1 mg·kg⁻¹ *iv*. The patient's lungs were mechanically ventilated with N₂O:O₂ (1:1) and isoflurane (0.7–1% end-tidal concentration) to maintain normocarbida. Intraoperatively the following variables were monitored: mean arterial pressure (MAP), heart rate (HR), arterial oxygen saturation (SpO₂), end tidal carbon dioxide (EtCO₂), airway and intra-abdominal pressures pre- and post-induction, and every 15 min thereafter until the end of surgery. A clinical response to intraoperative surgical stimulation was defined as an increase in either HR or MAP > 30% of baseline values after induction, and was treated with fentanyl 1 µg·kg⁻¹ *iv* boluses until restoration of hemodynamic parameters to baseline values. Muscle relaxation was maintained by appropriate doses of vecuronium until removal of the gallbladder. At the end of surgery, ondansetron 6 mg *iv* was administered, and residual neuromuscular block was antagonized with neostigmine and atropine. The cumulative dose of fentanyl and the time of the last fentanyl supplement before the end of surgery were recorded. In the postanesthesia care unit, quality of analgesia was assessed by a second trained observer who, along with the patient, was blinded to study group assignment. The VAS scores (linear 10 mm, starting from 0 = no pain to 10 = worst pain imaginable) were recorded at rest and with effort (coughing and at 30° sitting) 30 min postoperatively, and then at six hours intervals for 24 hr. After each VAS scoring interval, patients were asked if they required additional analgesia regardless of their VAS score. Patients were also instructed to request pain medication from the nurse whenever they required pain relief, and not to wait for their next scheduled pain assessment. Morphine 2–4 mg *iv* was titrated to patient comfort. No other analgesics or sedative medications were allowed for 24 hr after surgery. Diphenhydramine 25 mg *im prn* and metoclopramide 10 mg *im prn* were prescribed for itching and nausea/vomiting, respectively. The total amount of morphine administered, time to first morphine dose after surgery, hemodyna-

TABLE I Demographic data

	Group 1 (Control) (n = 30)	Group 2 (D1) (n = 30)	Group 3 (D2) (n = 30)
Sex (M/F)	3/27	4/26	2/28
Age (yr)	44.2 ± 4.3	44.1 ± 4.7	43.5 ± 5.3
Weight (kg)	64.4 ± 6.7	64.7 ± 6.3	65.2 ± 6.0
Duration of surgery (min)	58.7 ± 9.4	59.4 ± 10.3	60.8 ± 8.4

Data are presented as mean ± SD.

TABLE II Intra- and postoperative opioid consumption

	Group 1 (Control) (n = 30)	Group 2 (D1) (n = 30)	Group 3 (D2) (n = 30)
Intraoperative fentanyl (mg)	0.13 ± 0.03	0.13 ± 0.02	0.13 ± 0.02
Last fentanyl dose (min)	50.2 ± 4.4	51.4 ± 5.2	50.9 ± 4.9
First morphine dose (min)	48.5 ± 8.2	45.4 ± 7.8	49.8 ± 7.4
Postoperative morphine (mg)	39.8 ± 6.7	18.4 ± 4.2*	18.8 ± 4.4*

Data are presented as mean ± SD, **P* < 0.05 different from corresponding value of Group 1.

mic variables (MAP, HR, SpO₂) and occurrence of any intra- or postoperative adverse events, including, but not limited to itching, nausea/vomiting, respiratory depression (defined as respiratory rate < 12 per min), and radicular irritation were recorded.

Sample size calculation was based upon the variability of total morphine consumption during the first 24 hr postoperatively from 105 consecutive patients who had undergone uncomplicated laparoscopic cholecystectomy, receiving a similar anesthetic and analgesic treatment. Assuming $\alpha = 0.05$, and with standard deviation of the primary outcome measure of 5.5 mg, 30 patients per group were required to detect a difference of morphine consumption, within 2 mg (with 5% precision) of the population mean. Inter-group comparisons of demographic data were done using a Student's *t* test. Parametric data were compared by one-way analysis of variance (ANOVA) followed by Student's *t* test, and non-parametric data were analyzed with the Mann-Whitney U test. Results are expressed as mean ± SD. A value of *P* < 0.05 was considered statistically significant.

Results

Of the 94 patients studied, four patients were excluded from the analysis, two from Group 1 and one from Group D1 because of protocol violation and one patient in Group D2 who was converted to open

FIGURE 1 Postoperative visual analogue scale (VAS) scores at rest. Data are mean $\pm$ SD, * P < 0.05 different from corresponding value of group 1.

FIGURE 2 Postoperative visual analogue scale (VAS) scores during effort. Data are mean $\pm$ SD, * P < 0.05 different from corresponding value of group 1.

cholecystectomy. Patient characteristics in the remaining 90 patients were comparable with respect to age, weight and duration of surgery (Table I).

Cumulative intraoperative fentanyl requirements and timing of the last fentanyl dose were similar in all three groups. Times to first administration of morphine in the postoperative period were also similar amongst groups. The cumulative dose of morphine administered over 24 hr was lower in patients who

received epidural dexamethasone (Groups D1, D2) compared with the control group (P < 0.05, Table II). The percentage reduction in morphine consumption in Group D1 was 53.9% and in Group D2 was 52.9% during the first 24 hr, while VAS scores were similar in all groups up to the first six hours postoperatively. Visual analogue scale scores at 12 hr, 18 hr and 24 hr, during both rest and effort, were lower in Groups D1 and D2 compared to the control group (P < 0.05, Figures 1, 2, Table III). The MAP, HR, SpO₂, EtCO₂ values, airway and intra-abdominal pressures were similar amongst groups (Table IV). The frequencies of side effects during the 24 hr observation period were comparable in all three groups. One patient in Group D1 experienced nausea and vomiting; however, no patient in any group experienced itching, headache, respiratory depression or radicular irritation.

Discussion

The major finding of this study is that epidural dexamethasone 5 mg is effective in reducing postoperative pain and systemic opioid requirements following laparoscopic cholecystectomy. The postoperative analgesic efficacy of epidural dexamethasone was not enhanced by a single intraoperative dose of epidural bupivacaine.

The common methods used for analgesia after laparoscopic cholecystectomy produce short-term benefit and do not equate with earlier discharge or improved postoperative function. However, one trial evaluating multimodal analgesia suggested clinically relevant benefits can be achieved.³ Thoracic epidural analgesia with morphine-bupivacaine combination improves analgesia in the first 24 hr following laparoscopic cholecystectomy.⁴

Preoperative administration of dexamethasone by oral^{5,6} and *iv*^{7,8} routes has been shown to reduce overall pain scores and analgesic requirements in the postoperative period without any apparent adverse effect. Wang *et al.*⁹ showed that epidural administration of dexamethasone reduces the incidence and severity of

TABLE III VAS scores at rest and during effort and morphine consumption postoperatively at different time intervals

Time	Group 1 (Control) (n = 30)			Group 2 (D1) (n = 30)			Group 3 (D2) (n = 30)		
	VAS (rest)	VAS (effort)	Postoperative morphine (mg)	VAS (rest)	VAS (effort)	Postoperative morphine (mg)	VAS (rest)	VAS (effort)	Postoperative morphine (mg)
30 min.	4.7 $\pm$ 1.4	5.5 $\pm$ 2.0	-	3.8 $\pm$ 1.2	4.4 $\pm$ 1.5	-	3.6 $\pm$ 1.2	4.4 $\pm$ 1.8	-
6 hr	4.2 $\pm$ 1.6	4.8 $\pm$ 2.0	11.9 $\pm$ 2.0	3.6 $\pm$ 1.2	4.2 $\pm$ 2.2	9.6 $\pm$ 2.2	3.4 $\pm$ 1.4	4.0 $\pm$ 2.0	9.5 $\pm$ 2.1
12 hr	3.5 $\pm$ 1.2	4.2 $\pm$ 1.6	10.7 $\pm$ 1.8	1.6 $\pm$ 0.8*	2.1 $\pm$ 1.0*	4.1 $\pm$ 0.9*	1.4 $\pm$ 0.7*	1.9 $\pm$ 1.2*	9.2 $\pm$ 1.0*
18 hr	2.9 $\pm$ 0.8	3.4 $\pm$ 0.9	9.1 $\pm$ 1.5	1.4 $\pm$ 0.6*	1.6 $\pm$ 0.8*	2.4 $\pm$ 0.5*	1.2 $\pm$ 0.4*	1.4 $\pm$ 0.8*	2.4 $\pm$ 0.5*
24 hr	3.1 $\pm$ 1.2	3.6 $\pm$ 1.5	7.9 $\pm$ 1.3	1.5 $\pm$ 0.4*	1.8 $\pm$ 0.6*	2.2 $\pm$ 0.5*	1.4 $\pm$ 0.6*	1.6 $\pm$ 0.7*	2.3 $\pm$ 0.5*

Data are mean $\pm$ (SD), * P < 0.05 different from corresponding value of Group 1. VAS = visual analogue scale.

TABLE IV Oximetric, hemodynamic and pressure variables

	Group 1 (Control) (n = 30)	Group 2 (D1) (n = 30)	Group 3 (D2) (n = 30)
SpO ₂ (%)	99.2 ± 0.7	99.4 ± 0.6	99 ± 0.8
EtCO ₂ (mmHg)	35.8 ± 2.2	35.6 ± 2.4	36.2 ± 2.0
Heart rate (per min)	74.4 ± 4.2	76.3 ± 5.0	75.5 ± 4.5
Mean arterial pressure (mmHg)	92.3 ± 3.5	93.6 ± 3.2	92.8 ± 3.4
Intra abdominal pressure (mmHg)	12.2 ± 0.4	11.8 ± 0.5	12.0 ± 0.6
End-inspiratory pressure (cm H ₂ O)	24.4 ± 1.4	25.2 ± 1.2	24.8 ± 1.0

post-epidural backache following hemorrhoidectomy, although postoperative pain was not specifically evaluated in that clinical trial.

In a study of 500 hemorrhoidectomy patients who received epidural dexamethasone 5 mg Wang *et al.*⁹ demonstrated no adverse effects over a three-day follow-up period. In contrast Maillefert *et al.*¹⁷ found that a much larger dose of epidural dexamethasone (15 mg) may induce transient adrenal suppression. In an animal model, intrathecal infusion of low dose dexamethasone was shown to be safe, whereas higher doses were associated with inflammation of subarachnoid space.¹⁸ Injection of preservative-free medications is often advocated for epidural indications; however, intrathecal injection of methyl- and propyl paraben has been shown to be devoid of neurotoxic effects in both animal and human studies.^{19,20}

As no previous investigation has evaluated the efficacy of epidural dexamethasone for postoperative analgesia, we selected a dose of dexamethasone which has been shown previously to reduce post-epidural backache in patients undergoing hemorrhoidectomy.⁹ The timing of drug administration was similar that in a recent study evaluating the postoperative analgesic efficacy of *iv* dexamethasone in patients undergoing laparoscopic cholecystectomy.⁸ The selection of laparoscopic cholecystectomy for this study was important to standardize the level of postoperative surgical pain.⁸ The rationale for using *iv* dexamethasone 5 mg in a control group was to test whether the action of epidurally administered dexamethasone was at the spinal cord level, or at peripheral tissues after systemic absorption from the epidural space. The reason for using epidural dexamethasone 5 mg alone in Group D2 was to test whether the effect on pain scores in Group D1 was due to prolongation of the action of bupivacaine by dexamethasone.

In the present study, pain scores and total postoperative morphine consumption were lower in patients who received epidural dexamethasone (Groups D1, D2). The results are in keeping with the local application of corticosteroid at the surgical site following lumbar discectomy.^{21,22} In contrast to the findings from our study, intrathecal administration of corticosteroids in a rat model has been shown to have a mild effect on nociceptor-driven spinal sensitization.¹⁴ One possible explanation for this different response to neuraxial steroid administration is that the dose of methylprednisolone and triamcinolone in a rat model was insufficient to prevent the nociceptor-driven spinal sensitization. Blanloeil *et al.* reported that epidural steroids do not decrease pain after thoracotomy, although in their study the opioid consumption was less in patients who received epidural steroids.²³ Possible explanations to account for differences between these studies include sampling size differences and different steroids with different potencies.²⁴

The VAS pain scores in the epidural dexamethasone groups (D1, D2) were lower than observed in the control group in the current investigation. However, differences in the maximum analgesic benefits between groups D1 and D2 after six hours could have mechanistic implications. In a rat model of acute arthritis Ebersberger *et al.* demonstrated enhanced release of intraspinal prostaglandin E₂ after seven to eight hours, with maximum elevation of cyclo-oxygenase-2 protein levels 12 hr after the induction of inflammation.¹⁵ These findings are in keeping with reduced central sensitization.

Only one patient in Group D1 in our study experienced nausea and vomiting. The favourably low incidence of nausea and vomiting was probably multifactorial. Associated factors might have included the dexamethasone-ondansetron combination in the control group,^{25,26} use of ondansetron within the first six hours,²⁷ and improved analgesia and reduced opioid consumption²⁸ in Groups D1 and D2.

Although this study was not designed to address mechanisms, it is known that epidural dexamethasone may influence intraspinal prostaglandin formation. Acute noxious stimulation of peripheral tissues leads to sensitization of dorsal horn neurons of the spinal cord by the release of excitatory amino acids such as glutamate and aspartate. These amino acids activate N-methyl-D-aspartate receptors resulting in calcium ion influx. The increased intracellular calcium leads to activation of phospholipase A2, the rate-limiting enzyme in prostaglandin synthesis, which converts membrane phospholipids to arachidonic acid. Simultaneously, there is up-regulation of the expression of cyclo-oxy-

genase-2 in the spinal cord, leading to prostaglandin E_2 synthesis and a resultant hyperalgesic state.^{14,15} Corticosteroids are capable of reducing prostaglandin synthesis by inhibiting phospholipase A2 through the production of calcium-dependent phospholipid binding proteins called annexins,²⁹ and by the inhibition of cyclo-oxygenase-2 during inflammation.¹⁶ The dose of epidural dexamethasone required for the prevention of central sensitization and the time of onset and duration of action is not known.

In conclusion, thoracic epidural dexamethasone 5 mg reduces pain scores and opioid consumption following laparoscopic cholecystectomy, with no apparent side effects. Further investigations are warranted to evaluate the postoperative analgesic efficacy of dexamethasone for other types of surgical procedures.

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