Dexamethasone prophylaxis of nausea and vomiting after epidural morphine for post-Cesarean analgesia

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Purpose: To determine the minimum effective dose of dexamethasone in preventing nausea and vomiting associated with epidural morphine for post-Cesarean analgesia.

Method: One hundred and eighty parturients (n=45 in each of four groups) requiring epidural morphine for post-Cesarean analgesia were enrolled in this randomized, double-blinded, placebo-controlled study. At the end of surgery, parturients received either dexamethasone, at doses of 10 mg, 5 mg, 2.5 mg, or saline *iv*. Three milligrams epidural morphine were given to all parturients for postoperative analgesia. The incidence of PONV and side effects were estimated for 24 hr after delivery by blinded, trained nurse anesthetists.

Results: Parturients who received dexamethasone, either 10 mg or 5 mg were different from those who received saline alone in the following parameters: the total incidence of nausea and vomiting, incidence of > 4 vomiting episodes, number the of parturients requiring rescue antiemetics, and the total number of parturients with no vomiting and/or no antiemetic medication ($P < 0.05$ to $P < 0.01$). The differences between dexamethasone 10 mg and 5 mg were not significant. Dexamethasone 2.5 mg was partially effective.

Conclusion: Dexamethasone, 5 mg *iv*, is suggested as the minimum effective dose in preventing nausea and vomiting associated with epidural morphine for post-Cesarean analgesia.

Objectif : Déterminer la dose efficace minimale de dexaméthasone à utiliser pour prévenir les nausées et les vomissements liés à l'administration épidurale de morphine comme analgésie post-césarienne.

Méthode : Cent quatre-vingt parturientes (n=45 dans chacun des quatre groupes), nécessitant une analgésie épidurale post-césarienne avec morphine, ont participé à l'étude randomisée et à double insu contre placebo. Elles ont reçu, à la fin de l'opération, soit 10 mg, 5 mg ou 2,5 mg de dexaméthasone, soit une solution salée *iv*. Toutes ont reçu 3 mg de morphine comme analgésie postopératoire épidurale. L'incidence des NVPO et des effets secondaires a été évaluée pendant vingt-quatre heures après l'accouchement par des infirmières impartiales diplômées en anesthésie.

Résultats : Les parturientes qui ont reçu 10 mg ou 5 mg de dexaméthasone ont présenté des caractéristiques différentes de celles qui ont reçu le placebo pour les paramètres suivants: l'incidence totale de nausées et de vomissements, l'incidence d'épisodes de vomissements > 4, le nombre de patientes qui ont eu besoin d'antiémétiques de secours et le nombre total de parturientes sans vomissements et/ou sans médication antiémétique ($P < 0,05$à $P < 0,01$). Aucune différence significative n'était liée aux doses de 10 mg et de 5 mg de dexaméthasone. La dexaméthasone à 2,5 mg n'a été que partiellement efficace.

Conclusion : La dexaméthasone, administrée en doses de 5 mg *iv*, est suggérée comme la dose efficace minimale pour prévenir les nausées et les vomissements associés à l'analgésie épidurale post-césarienne avec de la morphine.

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EPIDURAL morphine has a potent and long-acting analgesic effect for postoperative pain when compared with epidural fentanyl and meperidine.[1–5] It is very convenient for clinical use and is widely accepted for postoperative analgesia, e.g., post-Cesarean analgesia.[1,4,5] However, despite its excellent analgesia properties, a high incidence of nausea and vomiting (30-65%) has been reported.[6–8] Among the antiemetics currently used, serotonin subtype 3 (5-HT_3) antagonists (e.g., ondansetron, granisetron) possess good efficacy, but high cost limits their widespread clinical application.[9,10] Other currently used antiemetics (e.g., anticholinergics, dopamine receptor antagonists, antihistamines) have side effects (e.g., restlessness, dry mouth, changes in blood pressure, and extrapyramidal symptoms).[6,7,11,12]

Dexamethasone is an effective antiemetic agent with minimal side effects after single dose administration.[13–18] It is effective in preventing chemotherapy-related emesis and postoperative nausea and vomiting (PONV).[1 8] Recently, we also found that dexamethasone (8 mg) was effective in preventing nausea and vomiting associated with epidural morphine for post-Cesarean analgesia.[1 4] Although effective, the minimum effective dose of dexamethasone for this purpose has not been determined. We, therefore, performed a randomized and double-blinded study to evaluate three doses of dexamethasone, compared with saline, in preventing epidural morphine-related nausea and vomiting in parturients undergoing Cesarean delivery.

Methods

The protocol was approved by the Hospital Committee for Human Investigation and informed consent was obtained from each parturient. One hundred and eighty parturients, ASA physical status I or II, 20-35 yr, scheduled for elective Cesarean delivery under epidural anesthesia were enrolled in a randomized, double-blinded, and placebo-controlled study. Parturients with a history of PONV, motion sickness or gastrointestinal disorders were excluded. The parturients with body weight < 50 kg or > 90 kg were also excluded. No premedication was given. Surgical anesthesia to T_4 was provided by 0.3 $ml \cdot kg^{-1}$ lidocaine 2% (with 1:100,000 epinephrine) followed by intermittent small-dose injections of lidocaine 2% (with epinephrine) as necessary through an epidural catheter in the L_{3-4} or L_{4-5} interspace. Five hundred milliliters lactated Ringer's solution were given intravenously before surgery to maintain a stable blood pressure. After delivery of the baby, routine use of 10 units oxytocin *iv* and 0.2 mg ergonovine *im* were given to all parturients to enhance uterine contraction. Estimated fluid deficits and maintenance requirements were replaced with lactated Ringer's solution intravenously. Intermittent *iv* boluses of ephedrine 8 to 10 mg were given, if necessary, for maintaining a stable blood pressure. Midazolam, 2.5 mg *iv*, was given, if necessary, to relieve the mental distress of mothers after delivery of the baby; no supplementary analgesia was given.

At the end of surgery, parturients were randomly assigned to four groups of 45 parturients to receive dexamethasone, at doses of 10 mg, 5 mg or 2.5 mg, or saline *iv*. The drug for injection was prepared as a 2 ml clear solution in identical syringes. One minute after injection, all parturients received 3 mg preservative-free morphine in 10 ml isotonic sodium chloride solution through the epidural catheter for postoperative analgesia. The randomization process and the identity of the study drugs were blinded from the parturients, the anesthesiologists during surgery, and the investigators who collected the postoperative data.

Postoperatively, parturients were observed for 24 hr. A team of trained nurse anesthetists without knowledge of which drugs the parturients had received collected the postoperative data. During the observation period, arterial blood pressure, heart rate, and respiratory rate were monitored every four hours except when parturients were sleep.

Nausea and vomiting was evaluated by the following parameters: the incidences of nausea and vomiting, episodes of vomiting, rescue antiemetics and successful prevention. For the purpose of data collection, retching (same as vomiting but without expulsion of gastric content) was considered as vomiting. A vomiting episode was defined by events of vomiting that occurred in a rapid sequence (<1 min between events). If the vomiting were separated by more than one minute, they were considered to be separate episodes. Vomiting which occurred more than four times within 24 hr was considered as severe vomiting. Rescue antiemetics (4 mg ondansetron *iv*) were given if vomiting occurred, or at the parturients' request. The treatment was repeated if necessary. No vomiting and no antiemetic medication during the 24-hr postoperative period was defined as successful prevention. This was also the primary efficacy end point of the study. The data of nausea and vomiting were collected every four hours, except when parturients were sleep, by direct questioning by a team of specially trained nurse anesthetists or by spontaneous complaint of the parturients.

Postoperative pain at the surgical wound was assessed with a 10-cm visual analog scale (VAS; 0= no pain to 10= most severe pain) score. When parturients complained of pain and requested analgesia, 20 mg

TABLE I Patient's demographics and operative characteristics

	Dexamethasone 10 mg	*Dexamethasone 5 mg*	*Dexamethasone 2.5 mg*	*Saline*
Number (n)	43	44	44	44
Age (yr)	28 ± 4	27 ± 3	27 ± 4	28 ± 5
Weight (kg)	70 ± 8	72 ± 9	71 ± 8	72 ± 9
Height (cm)	157 ± 3	156 ± 4	158 ± 4	157 ± 3
Pariety (n)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Duration of surgery (min)	54 ± 18	52 ± 20	48 ± 19	54 ± 21
Duration of anesthesia (min)	70 ± 22	72 ± 21	68 ± 23	74 ± 22
Total lidocaine administered (mg)	360 (320-420)	340 (300-420)	320 (300-400)	360 (320-440)
Total midazolam administered (mg)	0 (0-2.5)	0 (0-2.5)	0 (0-2.5)	0 (0-2.5)
Total ephedrine administered (mg)	10 (0-20)	8 (0-24)	8 (0-20)	10 (0-30)
Total *iv* fluid administered (ml)	1460 ± 210	1520 ± 210	1360 ± 180	1420 ± 190
Hospital stay (day)	6 ± 1	6 ± 1	7 ± 1	6 ± 1

Values are numbers, mean ± SD, or median (range).
No significant differences among groups.

TABLE II Postoperative wound pain at rest (VAS scores) and proportion of patients requiring rescue analgesic

Time (hr)	*Dexamethasone 10 mg*	*Dexamethasone 5 mg*	*Dexamethasone 2.5 mg*	*Saline*
4	2.1 ± 0.9	2.2 ± 1.0	2.1 ± 0.9	2.2 ± 1.1
8	1.8 ± 0.9	1.9 ± 1.1	2.1 ± 0.9	2.2 ± 1.2
20	2.2 ± 1.4	2.3 ± 1.2	2.4 ± 1.6	2.6 ± 1.5
24	2.1 ± 1.3	2.1 ± 1.2	2.2 ± 1.5	2.4 ± 1.4
Patients requiring rescue analgesic	11/43	10/44	11/44	14/44

Values are numbers or mean ± SD. VAS: visual analog scale;
No significant difference among groups.

TABLE III The evaluation of nausea and vomiting associated with epidural morphine for post-Cesarean analgesia

	Dexamethasone 10 mg	*Dexamethasone 5 mg*	*Dexamethasone 2.5 mg*	*Saline*
Number (n)	43	44	44	44
Nausea/vomiting				
Nausea	5 (12)	5 (11)	7 (16)	12 (27)
Vomiting	3 (7)	3 (7)	7 (16)	10 (23)
Total	8 (19)†	8 (18)†	11 (25)*	22 (50)
Vomiting episodes				
0-4 times	2 (5)	2 (5)	3 (7)	2 (5)
>4 times	1 (2)*	1 (2)*	1 (2)*	8 (18)
Rescue antiemetics	4 (9)*	5 (11)*	8 (18)	14 (32)
Successful prevention	39 (91)*	39 (89)*	36 (82)	30 (68)

Values are number of patients (%).
Successful prevention was defined as no vomiting and no antiemetic medication during a 24 hr postperative period.
†$P < 0.01$; *$P < 0.05$ when compared with saline group using a 4 x 2χ^2 test followed by a 2 x 2χ^2 test or Fisher's exact test, as appropriate.
No significant differences among Groups dexamethasone 10 mg and 5 mg.

tenoxicam *iv* (every 12 hr) was given. Pruritus was assessed on a three-point ordinal scale (0= none, 1= pruritus but only in a small area of the body, 2= generalized pruritus). Pruritus was treated with *im* diphenhydramine (20 mg every four hours as needed).

The occurrence of side effects accompanying dexamethasone usage, such as wound infection or delayed wound healing during their stay in hospital was evalu-

ated and reported by an obstetrician (Dr. Liu). Any other side effects were also recorded. Duration of hospital stay was recorded too.

Sample size was predetermined by using a power analysis based on the assumptions that (a) the total incidence of nausea and vomiting in the saline group would be 50%,[14] (b) a 40% reduction in the total incidence of nausea and vomiting (from 50% to 30%) in the treatment group would be of clinical relevance, and (c) α=0.05, ß=0.2.[19] The analysis showed that 40 parturients per group would be sufficient to detect the antiemetic effect of small dose of dexamethasone (2.5 mg).[19] A series of one-way analyses of variance were conducted to examine differences among the four groups with respect to parametric variables. If a significant difference was found, the Bonferroni t-test was used to detect the intergroup differences. The Kruskal-Wallis test was used to determine differences among the four groups with respect to nonparametric variables, followed by the Mann-Whitney *U* test for intergroup differences. Categorical variables were analyzed by using a series of $4 \times 2\chi^2$ tests to determine differences among the four groups, followed by $2 \times 2\chi^2$ tests or Fisher's exact tests, as appropriate, for intergroup differences. All follow-up analyses were corrected for the number of simultaneous contrasts using the Bonferroni adjustments. A P value < 0.05 was considered statistically significant.

Results

Of the 180 parturients enrolled in the study, five were withdrawn due to incomplete data collection. Therefore, 175 parturients completed the trial. There were no differences among groups with respect to age, weight, height, parity, duration of surgery and anesthesia, the consumptions of lidocaine, midazolam, ephedrine and *iv* fluid during surgery, and duration of hospital stay (Table I).

After surgery, all parturients received epidural 3 mg morphine for pain relief. All parturients reported low VAS pain scores and the differences among groups were not significant. In addition, the proportions of parturients requiring rescue analgesic among groups were not significantly different, neither (Table II).

Parturients who received dexamethasone, either 10 mg or 5 mg, were different from those who received saline alone in the following parameters: the total incidences of nausea and vomiting, incidence of > 4 vomiting episodes, the number of parturients requiring rescue antiemetics, and the the total number of parturients with no vomiting and/or no antiemetic medication (Table III). The differences between dexamethasone 10 mg and 5 mg were not statistically significant. Dexamethasone 2.5 mg was only partially effective.

The incidence of pruritus among groups was not different and was in the range of 41 to 47% in the dexamethasone groups and 43% in the saline group. The severity of pruritus among groups was not significant. Nine to 15% of parturients in the dexamethasone groups and 14% of parturients in the saline group requested *im* diphenhydramine for the management of pruritus. No other side effect associated with the usage of dexamethasone was found.

Discussion

Many reports have suggested the use of 8 to 10 mg dexamethasone as a prophylactic antiemetic agent for PONV.[13–18] The antiemetic effect of 8 to 10 mg dexamethasone is equal to that of 4 mg ondansetron[10,18] and 1.25 mg droperidol.[13] Recently, we have also shown that 8 mg dexamethasone reduced the incidence of nausea and vomiting related to epidural morphine in the treatment of post-Cesarean pain.[14] However, the minimum effective dose of dexamethasone for this purpose was not determined. In the current study, We found that 10 mg and 5 mg dexamethasone were more effective than saline in preventing nausea and vomiting associated with epidural morphine for post-Cesarean analgesia. The differences between 10 mg and 5 mg dexamethasone were not statistically significant. Dexamethasone 2.5 mg was partially effective. Dexamethasone 5 mg *iv* may be the minimum effective dose for this purpose.

We also found that dexamethasone did not influence the efficacy of epidural morphine-related analgesia. Parturients receiving 2.5 mg, 5 mg or 10 mg dexamethasone requested similar amounts of rescue analgesic and reported similar intensities of postoperative pain. Besides, dexamethasone did not influence the occurrence of pruritus related to epidural morphine for post-Cesarean analgesia.

The exact mechanism by which epidural morphine exerts an emetic action is alleged to be activation of opioid receptors in the chemoreceptor trigger zone of the fourth ventricle caused by cephalad migration of the morphine.[8] However, the exact mechanism by which dexamethasone, a glucocorticoid, exerts an antiemetic action after epidural morphine is not known.[18] Glucocorticoids have been shown to have various effects on the central nervous system; they regulate transmitter levels, receptor densities, signal transduction, and neuronal configuration.[20,21] In the nucleus of the solitary tract, the nucleus of raphe, and the area postrema, numerous glucocoriticoid receptors are found.[21,22] These nuclei are well known to have consid-

erable neuronal activities on the regulation of nauseating and vomiting responses.[8,23] Dexamethasone may exert its antiemetic action through these nuclei.

Some factors which may interfere with the interpretation of the study result, such as consumptions of ephedrine, midazolam, diphenhydramine and *iv* fluid, were also evaluated in our study.[23,24] We found that the intraoperative consumptions of ephedrine, midazolam and *iv* fluid were similar among groups. In addition, the use of diphenhydramine among groups for the treatment of pruritus was also similar. Therefore, differences in the occurrence of nausea and vomiting among the groups can be attributed to the study drugs.

In a previous study, we found that *iv* dexamethasone has a delayed onset of action for both nausea and vomiting.[25] The lag time was about two hours.[25] In patients receiving epidural morphine, the occurrence of nausea and vomiting is usually two to four hours after medication.[1,8] In our study, *iv* dexamethasone was given one minute before the administration of epidural morphine. Under this design, dexamethasone was considered to be an active antiemetic if the dosage was appropriate.

Multiple-dose corticosteroid therapy (>1 week) may cause side effects, such as increased risk of infection, glucose intolerance, delayed wound healing, superficial ulceration of gastric mucosa, avascular necrosis of femoral head, and adrenal supression.[20,26] However, these side effects are not found after a single dose of dexamethasone therapy.[13–18] In the current study, a single dose of 2.5 to 10 mg dexamethasone did not cause wound infection or delay wound healing. In addition, no other side effects were also found after the usage of a single dose of dexamethasone.

In conclusion, 10 mg and 5 mg dexamethasone were more effective than saline in preventing epidural morphine-related nausea and vomiting in parturients undergoing Cesarean delivery. The difference between dexamethasone 10 mg and 5 mg was not significant. Dexamethasone 2.5 mg was partial effective. We suggest that dexamethasone 5 mg *iv* is the minimum effective dose for this purpose.

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