Epidural naloxone reduces pruritus and nausea without affecting analgesia by epidural morphine in bupivacaine

Jong H. Choi MD,
Jaimin Lee MD,
Jeong H. Choi MD,
Michael J. Bishop MD,*

Purpose: To determine whether epidural naloxone preserved analgesia while minimizing side effects caused by epidural morphine.

Methods: Eighty patients undergoing combined epidural and general anesthesia for hysterectomy were randomly assigned to one of four groups. All received 2 mg epidural morphine bolus one hour before the end of surgery and a continuous epidural infusion was started containing 4 mg morphine in 100 ml bupivacaine 0.125% with either no naloxone (Group 1, n=20), 0.083 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of naloxone (Group 2, n=20), 0.125 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of naloxone (Group 3, n=20) or 0.167 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of naloxone (Group 4, n=20). Analgesia and side effects were evaluated by blinded observers.

Results: The combination of epidural morphine and bupivacaine provided good analgesia. Eight hours after the end of surgery, the pain score in the group receiving the highest dose of naloxone was lower than in the control group (VAS 1.2 *vs* 2.0, $P < 0.05$) but there was less pruritus in the high-dose naloxone group (itching score 1.3 *vs* 1.9, $P < 0.05$). Pain scores were no different in any of the naloxone groups from the control group. Itching was less in both of the higher dose naloxone groups ($P < 0.05$ at 8, 16, and 32 hours). The incidence of vomiting in the control group was 40% *vs* 5% for high dose naloxone group ($P < 0.05$).

Conclusions: Epidural naloxone reduced morphine-induced side effects in dose-dependent fashion without reversal of the analgesic effect.

Objectif : Déterminer si la naloxone épidurale préserve l'analgésie tout en réduisant les effets secondaires de la morphine épidurale.

Méthode : Quatre-vingt patientes devant subir une hystérectomie avec une anesthésie péridurale et générale combinée ont été réparties au hasard en quatre groupes. Toutes ont reçu un bolus de 2 mg de morphine épidurale une heure avant la fin de l'opération et une perfusion épidurale continue a été amorcée avec 4 mg de morphine dans 100 ml de bupivacaïne 0,125 % sans naloxone (Groupe 1, n = 20), avec 0,083$\mu g \cdot kg^{-1} \cdot h^{-1}$ de naloxone (Groupe 2, n = 20), ou 0,125$\mu g \cdot kg^{-1} \cdot h^{-1}$ de naloxone (Groupe 3, n = 20) ou 0,167$\mu g \cdot kg^{-1} \cdot h^{-1}$ de naloxone (Groupe 4, n = 20). L'analgésie et les effets secondaires ont été évalués par des observateurs impartiaux.

Résultats : La combinaison de morphine épidurale et de bupivacaïne a fourni une bonne analgésie. Huit heures après la fin de l'intervention chirurgicale, le score de douleur chez les patientes qui ont reçu la plus forte dose de naloxone était plus bas que celui des patientes du groupe témoin (EVA 1,2 *vs* 2,0, $P < 0,05$), et il y avait moins de prurit chez les patientes ayant reçu la dose élevée de naloxone (score de 1,3 *vs* 1,9, $P< 0,05$). Les scores de douleur n'ont pas montré de différence intergroupe. Le prurit était moins marqué chez les patientes des deux groupes qui ont reçu les doses plus élevées de naloxone ($P < 0,05$ à 8, 16, et 32 heures). L'incidence des vomissements chez les patientes témoins a été de 40 % *vs* 5 % pour les femmes ayant reçu une forte dose de naloxone $P < 0,05$).

Conclusion : L'administration épidurale de naloxone réduit les effets secondaires induits par la morphine d'une façon qui dépend de la dose sans renverser l'effet de l'analgésique.

From the Department of Anesthesiology, Kangnam Saint Mary's Hospital, 505 Banpo-dong, Seocho-gu, Seoul, Korea and the Puget Sound Veterans Affairs Medical Center* and the University of Washington School of Medicine, Seattle, Washington.

Address correspondence to: Dr. Jaimin Lee, 137-040, Department of Anesthesiology, Kangnam Saint Mary's Hospital, 505 Banpo-dong, Seocho-gu, Seoul, Korea. Phone: 82-2-590-1545; Fax: 82-2-537-1951; E-mail: jmlee@cmc.cuk.ac.kr

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POSTOPERATIVE epidural pain control has become an important part of acute pain management because of its effects on postoperative patient recovery. Benefits of the technique include preservation of pulmonary function, the cough reflex, and motor function, and inhibition of the stress response to pain.[1] However, epidural morphine has several adverse effects including respiratory depression, itching, and nausea. This has led to attempts to combine epidural morphine administration with epidural administration of drugs such as butorphanol and droperidol in the hope of minimizing side effects.

Small doses of the opioid antagonist naloxone administered intravenously maintain analgesia and reduce epidural morphine-induced side effects effectively.[2] In rabbits, intraspinal naloxone effectively inhibits visceromotor responses to morphine.[3] The analgesic effects of epidural morphine can be inhibited in rats by epidural naloxone.[4] So far, however, clinical experiments have not established the effect of epidural naloxone on analgesic effect of morphine and the incidence of side effects.

We hypothesized that there was a relationship between the epidural naloxone doses that would minimize side effects in patients receiving epidural pain control with morphine and bupivacaine without reversing analgesia.

Methods

The protocol was approved by the Human Subjects Review Board of Catholic Medical Center's Kangnam Saint Mary Hospital. Eighty patients provided written consent for the study and all were scheduled to undergo hysterectomy with a Pfannenstiel incision. Patients weighed 50 - 60 kg and had a height of 150 - 160 cm. Patients were excluded if they had any pre-existing cardio-pulmonary, hepatic, renal, or endocrine disease.

After identification of the epidural space using the loss of resistance technique, a 20 gauge epidural catheter was placed between the 3rd and 4th lumbar vertebrae and fixed three centimeters into the epidural space. An initial dose of 10 ml bupivacaine 0.33% was then injected. Patients underwent anesthetic induction and tracheal intubation after 4 $mg \cdot kg^{-1}$ thiopental and 1 $mg \cdot kg^{-1}$ succinylcholine. Muscle relaxation was induced with 0.08 $mg \cdot kg^{-1}$ vecuronium and general anesthesia was maintained with enflurane <0.5% end-tidal and nitrous oxide 60%.

Five minutes after induction, 5 ml bupivacaine 0.33% were again administered via the epidural catheter and, at ten minutes after induction, an additional 3 - 5 ml bupivacaine were administered. Patients then received between 1/2 and 1/3 of the initial dosage (15 ml) at one hour intervals until the end of the surgery.

As the surgeons started to close the abdominal cavity, each patient was given 2 mg morphine into the epidural catheter. A continuous epidural infusion was then initiated by attaching Two-day Infusors™ (Baxter, USA), containing 4 mg morphine in 100 ml bupivacaine 0.125%.

Patients were randomly allocated into four groups, each of which received a different medication mixture via the Two-day Infusors. Group 1 received 80 μg morphine in 2 ml bupivacaine 0.125% per hour. Group 2 received the same mixture, but with the addition of 0.083 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of naloxone. Groups 3 and 4 were identical to Group 2 except that the naloxone infusion rate was 0.125 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for Group 3, and 0.167 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for Group 4.

Visual Analog Scales (VAS)[5] were employed to assess postoperative pain at 2, 4, 8, 16, 32, and 48 hr. Nausea, itching, somnolence and respiratory depression were assessed using the evaluation scores noted in Table I. The assessment was carried out by anesthesiologists who had not been involved in care of the patients and who were blinded to the group assignment.

The effects of the treatments were evaluated at each point using the Kruskal-Wallis statistic to determine whether significant differences existed among groups and specific inter-group differences were identified using the Mann-Whitney U test. The incidence of vomiting was compared using Fisher's exact test to compare groups pairwise.

Results

There were no differences among groups in age, height or weight (Table II). The outcome of data analyses for each group at each time point is shown in Table III.

Pain

All four groups experienced good pain control with the highest VAS scores at four hours after the end of surgery (Figure 1). Group 4, the highest naloxone dose, had lower VAS scores compared with Group 1 at 8, 16 and 32 hr postoperatively ($P < 0.05$).

Itch

Groups 3 and 4 had less itching than did Groups 1 and 2, with the difference persisting throughout most of the study (Figure 2) ($P < 0.05$ at 8, 16, 32 hr for Groups 3 and 4 *vs* Group 1). Even at the lowest dose of naloxone (Group 2), some benefit was derived in relieving the itching ($P < 0.05$ at 32 hr *vs* Group 1).

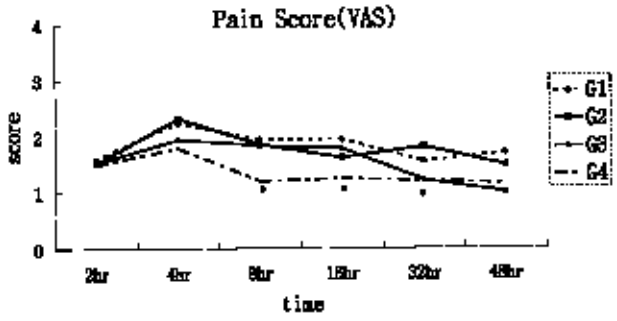

FIGURE 1 The change of VAS postoperatively among the four groups. All symbols and corresponding lines represent the mean. *($P < 0.05$) different from control group (Group 1).

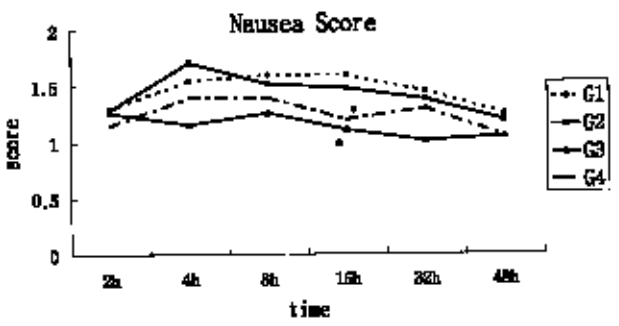

FIGURE 3 The change of nausea score postoperatively among the four groups. All symbols and corresponding lines represent the mean.
* ($P < 0.05$) different from control group (Group 1).

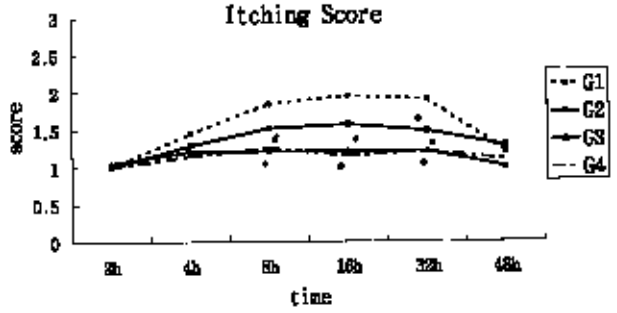

FIGURE 2 The change of itching score postoperatively among the four groups. All symbols and corresponding lines represent the mean.
* ($P < 0.05$) different from control group (Group 1).

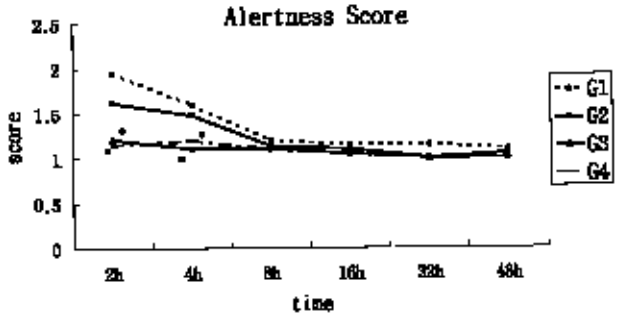

FIGURE 4 The change of alertness score postoperatively among the four groups. All symbols and corresponding lines represent the mean.
*($P < 0.05$) different from control group (Group 1).

Nausea

Groups 3 and 4 reported less nausea at 16 hr than did group 1 ($P < 0.05$)(Figure 3). The incidence of vomiting or retching at some point in the postoperative course was 40%, 25%, 15%, and 5% for groups 1 through 4 respectively ($P < 0.05$ for Group 4 *vs* Group 1 by Fisher's exact test).

Alertness

Alertness scores were excellent for all groups throughout the study although statistically significantly better over the first four hours in Groups 3 and 4 (Figure 4) ($P < 0.05$ at two and four hours).

Respiratory depression

The four groups showed no difference during the 48 hr, and none of the patients experienced respiratory depression (respiratory rate < 8 bpm).

Discussion

The important finding of this study is that the addition of naloxone to a postoperative epidural infusion of bupivacaine and morphine can reduce nausea, vomiting, and itching while preserving analgesia.

Not surprisingly, pain scores were low in all of the patients since the combination of bupivacaine plus morphine is an effective analgesic. We found no reduction in efficacy in patients receiving naloxone and epidural naloxone actually improved analgesia at the highest dose. We speculate that this is due to reduced side effects producing greater comfort. The beneficial effects of naloxone were dose related with higher doses reducing itching more than lower doses.

Our study builds on other efforts to limit the side effects of epidural morphine while maintaining good analgesia. These have included administering non-steroidal anti-inflammatory drugs plus morphine, ß-2

adrenergic agonists plus morphine, and low concentrations of local anesthetics plus morphine.[6] Klahsen *et al.*[7] and Isosu *et al.*[8] found that epidural droperidol could reduce morphine-induced nausea and vomiting. However, continuous epidural administration of droperidol may trigger such side effects as dystonia and akathisia.[9]

TABLE I Scoring system of postoperative checkpoints

Nausea/Vomiting	1 : no nausea
	2 : complains of nausea, but tolerable
	3 : severe nausea, needs medication
Itching	1 : no itching
	2 : complain itching, but tolerable
	3 : severe itching, needs medication
Alertness	1 : clear mentality
	2 : good response to verbal command, but drowsy
	3 : poor response to repeated verbal command
Respiratory depression	1 : none detected
	2 : exist (RR < 8 min^{-1})

TABLE II Demographic data of the patients

	Age	*BW(kg)*	*Height(cm)*
Group 1	35.7±9.3	53.5±3.3	155.7±3.4
Group 2	40.5±9.8	56.8±3.2	157.3±2.1
Group 3	38.3±7.8	55.9±3.7	153.2±2.6
Group 4	42.4±8.6	54.8±4.7	153.6±2.9

Values are mean SD
No significant difference among groups

Epidural administration of the agonist-antagonist butorphanol, which acts as an antagonist at mu receptors but as an agonist at kappa receptors, reduced itching and nausea, and maintained analgesia without causing somnolence or respiratory depression.[10,11] However, an increased incidence of altered consciousness rather than reduced side effects was noted in another report among patients who had Cesarean section and were given morphine and butorphanol.[12] Cohen *et al.*[13] found that intravenous administration of nalbuphine was more effective than naloxone in reducing morphine-induced side effects such as itchiness and nausea, but its effects were of short duration and it also resulted in increased sedation.

The efficacy of naloxone in reducing nausea and vomiting while preserving the analgesic effects of epidural morphine is well documented.[2] However, titration of the dose is critical since excess naloxone may reverse analgesia and is capable of inducing hyperalgesia.[14,15] Little is known about the dose-response relationship of naloxone when administered into the epidural space. Epidural administration of naloxone in mice reverses the analgesic effect of epidural morphine, but the effects on other actions of morphine are not known nor are the effects in humans documented.[3] Our study found a dose range for epidural naloxone that preserves analgesia while minimizing side effects.

We were surprised to find better analgesic effects in Group 4 patients despite the higher dose of naloxone. Although this could be the result of some partial agonist effect from naloxone,[16,17] it may also be a reflection of greater overall comfort in the patients because of less nausea and itching.

TABLE III The outcome of data analyses

		2 hr	*4 hr*	*8 hr*	*16 hr*	*32 hr*	*48 hr*
Pain	Group 1	1.60±0.99	2.25±1.25	1.95±0.83	1.95±0.94	1.55±0.60	1.70±0.98
	Group 2	1.52±0.81	2.33±1.15	1.86±1.01	1.62±0.86	1.81.±1.03	1.48±0.75
	Group 3	1.53±0.84	1.95±1.02	1.84±0.89	1.79±0.79	1.21±0.42	1.00±0.00
	Group 4	1.50±0.76	1.80±1.01	1.20±0.41*	1.25±0.44*	1.20±0.70*	1.15±0.37
Itch	Group 1	1.00±0.00	1.45±0.51	1.85±0.49	1.95±0.60	1.90±0.31	1.20±0.41
	Group 2	1.00±0.00	1.29±0.46	1.52±0.60	1.57±0.51	1.48±0.52*	1.28±0.46
	Group 3	1.05±0.23	1.21±0.46	1.21±0.30*	1.21±0.50*	1.21±0.25*	1.00±0.00
	Group 4	1.00±0.00	1.15±0.37	1.25±0.44*	1.15±0.37*	1.20±0.41*	1.10±0.31
Nausea	Group 1	1.30±0.57	1.55±0.82	1.60±0.75	1.60±0.68	1.45±0.76	1.25±0.55
	Group 2	1.29±0.64	1.71±0.64	1.52±0.68	1.48±0.60	1.38±0.59	1.19±0.51
	Group 3	1.29±0.56	1.16±0.37	1.26±0.65	1.11±0.32*	1.01±0.00	1.05±0.23
	Group 4	1.15±0.37	1.40±0.50	1.40±0.60	1.20±0.40*	1.30±0.57	1.05±0.22
Alertness	Group 1	1.95±0.83	1.60±0.50	1.20±0.41	1.15±0.37	1.15±0.37	1.10±0.31
	Group 2	1.62±0.67	1.48±0.51	1.14±0.36	1.10±0.30	1.00±0.00	1.00±0.00
	Group 3	1.21±0.42*	1.11±0.32*	1.11±0.32	1.05±0.23	1.00±0.00	1.05±0.23
	Group 4	1.15±0.49*	1.20±0.41*	1.10±0.31	1.05±0.22	1.00±0.00	1.00±0.00

Values are mean ±SD
* : $P < 0.05$ *vs* Group 1

We conclude that epidural administration of naloxone can preserve analgesia while minimizing itching, nausea, pruritus and somnoloence. The highest dose used - 0.167 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ - gave the best results, but we cannot be certain whether this is the ideal dose or whether higher doses might produce fewer side effects without interfering with analgesia.

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