Epidural naloxone reduces intestinal hypomotility but not analgesia of epidural morphine

Jaemin Lee MD, Jae Y. Shim MD, Jeong H. Choi MD, Eun S. Kim MD, Ou K. Kwon MD, Dong E. Moon MD, Jong H. Choi MD, Michael J. Bishop MD*

Purpose: Epidural morphine is associated with decreased bowel motility and increased transit time. Low doses of intravenous naloxone reduce morphine-induced pruritus without reversing analgesia, but the effect of epidural naloxone on bowel motility has not been studied. Therefore we evaluated bowel motility and analgesia when naloxone was co-administered with morphine into the epidural space.

Methods: Forty-three patients having combined thoracic epidural and general anesthesia for subtotal gastrectomy were randomly assigned to one of two study groups. All received a bolus dose of 3 mg epidural morphine at the beginning of surgery, followed by a continuous epidural infusion containing 3 mg morphine in 100 ml bupivacaine 0.125% with either no naloxone (control group, n = 18) or a calculated dose of 0.208 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of naloxone (experimental group, n = 25) for 48 hr. We measured the time to the first postoperative passage of flatus and feces to evaluate the restoration of bowel function, and visual analog scales (VAS) for pain during rest and movement. Scores were assessed at 2, 4, 8, 16, 24, 36 and 48 hr postoperatively.

Results: The experimental group had a shorter time to the first postoperative passage of flatus (51.9 ± 16.6 hr *vs* 87.0 ± 19.5 hr, $P < 0.001$) and feces (95.3 ± 25.0 hr *vs* 132.9 ± 29.4 hr, $P < 0.001$). No differences were found in either resting or active VAS between the two groups.

Conclusion: Epidural naloxone reduces epidural morphine-induced intestinal hypomotility without reversing its analgesic effects.

Objectif : L'administration péridurale de morphine est associée à une baisse de la motilité intestinale et à une augmentation de la durée du transit. De faibles doses de naloxone intraveineuse réduisent le prurit induit par la morphine sans renverser l'analgésie, mais l'effet de l'administration péridurale de naloxone sur la motilité intestinale n'a pas encore été étudié. C'est pourquoi nous avons évalué cette action et l'analgésie de la naloxone administrée avec de la morphine dans l'espace péridural.

Méthode : Quarante-trois patients qui recevaient une anesthésie péridurale thoracique et générale combinée, pour une gastrectomie partielle, ont été répartis au hasard en deux groupes. Tous ont reçu un bolus de 3 mg de morphine péridurale au début de l'intervention, suivi d'une perfusion péridurale continue de 3 mg de morphine dans 100 ml de bupivacaïne à 0,125 % sans naloxone (groupe témoin, n = 18) ou avec une dose calculée de 0,208 $\mu g \cdot kg^{-1} \cdot h^{-1}$ de naloxone (groupe expérimental, n = 25) pendant 48 h. Nous avons mesuré le temps écoulé avant la première expulsion des gaz intestinaux et des selles afin d'évaluer la restauration de la fonction intestinale et mesuré les scores de douleur à l'aide de l'échelle visuelle analogique (EVA), au repos et pendant le mouvement. Les scores postopératoires ont été relevés à 2, 4, 8, 16, 24, 36 et à 48 h.

Résultats : Dans le groupe expérimental, le temps précédant le premier passage postopératoire des gaz (51,9 ± 16,6 h *vs* 87,0 ± 19,5 h, $P < 0,001$) et des selles (95,3 ± 25,0 h) a été plus court comparé au groupe témoin (132,9 ± 29,4 h, $P < 0,001$). Aucune différence intergroupe n'a été observée aux scores de l'EVA obtenus au repos ou pendant le mouvement.

Conclusion : La naloxone péridurale réduit l'hypomotilité intestinale induite par la morphine péridurale sans renverser ses effets analgésiques.

From the Department of Anesthesiology, Kangnam Saint Mary's Hospital, 505 Banpo-dong, Seocho-gu, Seoul, Korea. 137-040, and Puget Sound Veterans Affairs Medical Center* and the University of Washington School of Medicine, Seattle, Washington.

Address correspondence to: Dr. Jong H. Choi; Phone: 82-2-590-1545; Fax: 82-2-537-1951; E-mail: jchoi@cmc.cuk.ac.kr

Accepted for publication September 22, 2000.

CO-ADMINISTRATION of epidural morphine and bupivacaine is an effective method of postoperative pain control that maintains analgesia while reducing the side effects when compared with epidural morphine alone.[1] Postoperative gastric emptying is delayed after epidural analgesia with morphine compared with epidural bupivacaine[2,3] and, for this reason, some surgeons are not inclined to use an epidural for postoperative pain control.

Choi *et al.*[4] found in a recent report that epidural naloxone preserves analgesia while minimizing the side effects of itching and nausea. Animal experiments have shown that an opioid antagonist such as naloxone reverses the morphine-induced decline in intestinal motility,[5] and clinical experiments have also documented that intravenous or subcutaneous injection of naloxone can antagonize opioid-related intestinal hypomotility.[6,7]

The effect of epidural naloxone on human intestinal hypomotility has not been studied. We hypothesized that co-administration of naloxone would preserve both analgesia and intestinal motility when epidural bupivacaine and morphine are used for pain control after gastrectomy.

Methods

The experiment was carried out on 43 ASA 1-2 patients with stomach cancer, without any pre-existing cardio-pulmonary, endocrine, hepatic, or renal disease. The protocol was approved by the Human Subjects Review Board of Catholic Medical Center's Kangnam Saint Mary's Hospital and all the patients provided written consent for the study. Patients weighed 60~70 kg and had a height of 160~170 cm. In order to eliminate interference from different surgical techniques, the experiment was undertaken in patients of a single surgeon performing subtotal gastrectomy and Billroth II anastomosis.

After identification of the epidural space between the 8th and 9th thoracic vertebrae using the loss of resistance technique, a 20 gauge epidural catheter was placed three centimeters cephalad into the epidural space with patients in a left lateral decubitus position. Sensory block at least to the dermatome of the 6th thoracic vertebra in the supine position was confirmed in each case. 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 by 0.08 $mg \cdot kg^{-1}$ pancuronium, and general anesthesia was maintained with 3 $L \cdot min^{-1}$ N_2O and 2 $L \cdot min^{-1}$ O_2 using a semi-closed circle system. Controlled ventilation was conducted with a tidal volume of 10 $ml \cdot kg^{-1}$, I:E ratio at 1:2, and respiratory rate of 8 / min ~ 12 / min.

Ten minutes after induction of general anesthesia, 3 mg morphine were administered via the epidural catheter. Patients then received 5 ml bupivacaine 0.33% at one hour intervals until the end of surgery. When the surgeons closed the peritoneum, a continuous infusor (Baxter®, USA) was attached to the epidural catheter for 48 hr postoperative pain control.

Patients were randomly assigned to one of two groups by flipping a coin; naloxone was added to the continuous infusor in the treatment group, but not in the control group. The control group (n=18) received 3 mg morphine in 100 ml bupivacaine 0.125% at 2 $ml \cdot hr^{-1}$ for two days via the infusor. The treatment group (n=25) received the same mixture, but with the addition of 0.208 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ naloxone using the same method.

We used Visual Analog Scales (VAS; 10 cm) to assess postoperative pain at 2, 4, 8, 16, 24, 36, and 48 hr, both at rest and after coughing. In order to evaluate the recovery of intestinal motility, the times to the first postoperative passage of flatus and feces were measured as well. All assessments were carried out by anesthesiologists who had not taken part in the experiment and were blinded to the group assignment.

Pain scales were analyzed to identify inter-group differences using the Mann-Whitney U test. The independent t test carried out for difference in intestinal motility times were analyzed using Student's t test for independent data.

Results

There were no differences between the two groups in age, weight or height. (Table)

Evaluation of postoperative pain control

At rest, the highest VAS scores were recorded at two hours after surgery and the scores decreased steadily thereafter. The average VAS score was below 3.2 at all points of evaluation for both groups, indicating satisfactory levels of pain control. Comparison of the two groups at each evaluation point showed no significant inter-group differences. (Figure 1)

TABLE Demographic data

	Age(yr)	*BW(kg)*	*Height(cm)*
Control Group	52.5 ± 11.2	64.2 ± 6.9	164.4 ± 8.5
Experimental Group	53.4 ± 10.8	63.6 ± 6.4	162.0 ± 6.7

Values are mean ± SD

No significant difference between groups

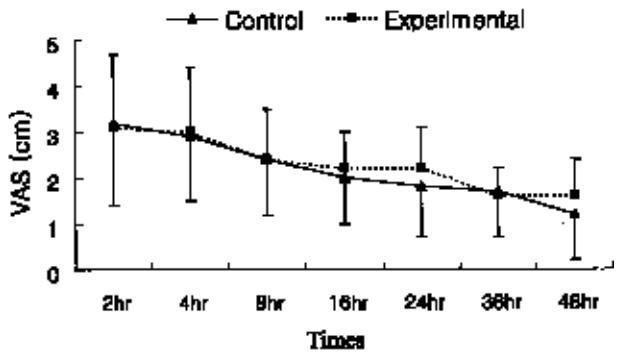

FIGURE 1 Postoperative resting VAS(visual analog scale) scores at 2, 4, 8, 16, 24, 36 and 48 hr after the surgery. Values are mean ± SD. No significance could be found between two groups.

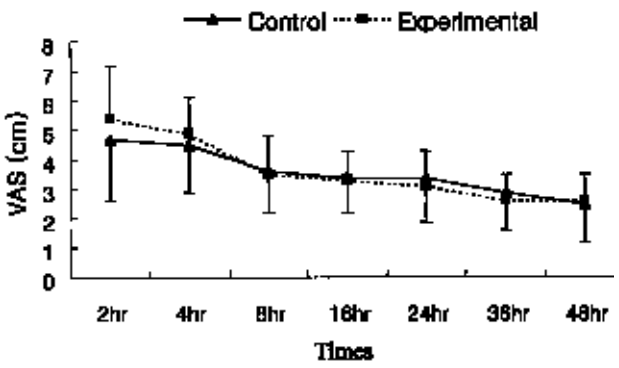

FIGURE 2 Postoperative movement VAS(visual analog scale) scores at 2, 4, 8, 16, 24, 36 and 48 hr after the surgery. Values are mean ± SD. No significance could be found between two groups.

During coughing, VAS scores were again highest at two hours after the end of surgery and showed a decline afterwards. At all evaluation points with the exception of two and four hours, the average VAS score was < 3.6. Comparison of the two groups at each evaluation point again showed no significant inter-group differences. (Figure 2)

Assessment of recovery in intestinal motility

The time to the first postoperative passage of flatus was 87.0 ± 19.5 hr for the control group (mean ± SD), and 51.9 ± 16.6 hr for the experimental group ($P < 0.001$). The time to the first feces was 132.9 ± 29.4 hr for the control group and 95.3 ± 25.0 hr for the experimental group ($P < 0.001$). (Figure 3)

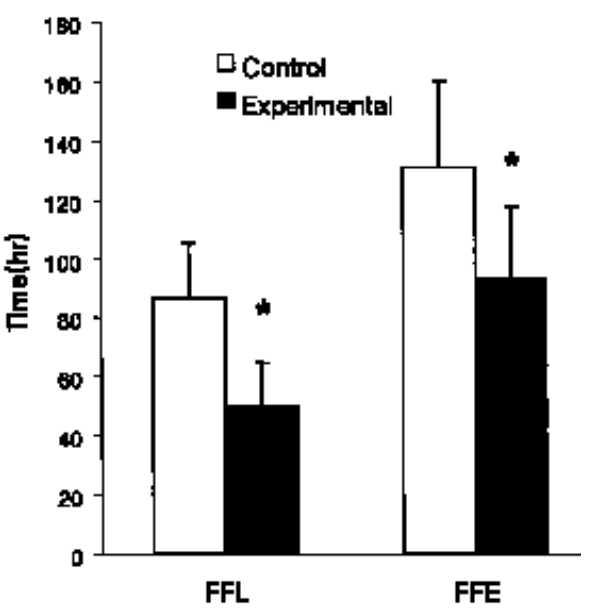

FIGURE 3 Time to postoperative first flatus and first feces of the two groups. Values are mean ± SD. FFL: first flatus, FFE: first feces. *$P < 0.001$ compared with control group.

Discussion

Co-administration of morphine and bupivacaine is widely used as an effective method of postoperative pain control. Despite its benefits, morphine-induced side-effects including respiratory depression, nausea, and vomiting restrict its use in some cases. However, Choi *et al.*[4] reported that naloxone co-administered with morphine via the epidural route reduced nausea, vomiting and itching while not reversing analgesia and that, at certain doses, naloxone improved the analgesic effect. In our assessment of VAS scores, the dose and the method of administration for morphine and bupivacaine were found to be safe and effective for post-gastrectomy pain control. The experimental group that received naloxone in addition also showed good results for postoperative pain control, confirming that naloxone used in appropriate quantities will not antagonize the analgesic effect of morphine.

The VAS during coughing was 1 or 2 points higher than at rest until four hours postoperatively, but was not different thereafter. This difference probably occurs because afferent sensory transmission from the surgical wound differs during rest and movement and, as a result, a qualitatively different evaluation is made.[8] Since intestinal motility has a high correlation with

postoperative ambulation, it is essential to carry out an inter-group comparison of analgesia during movement as well as at rest.

Morphine and bupivacaine influence postoperative intestinal motility in different ways. Bupivacaine has been reported to relieve the postoperative ileus by blocking inhibitory spinal reflexes to the gut that are activated by abdominal surgery.[2,9] Morphine, on the other hand, has either a direct action on colonic smooth muscle or a presynaptic inhibitory action at a ganglionic site in non-adrenergic inhibitory nerves.[10] Its influence on intestinal motility is a result of its action on opioid receptors both at the supraspinal and spinal levels.[11] The gastrointestinal effects of opioids are mediated primarily by *mu* receptors at the supraspinal level while both *delta* and *mu* receptors mediate this effect at the spinal level.[12] Morphine inhibits the intestinal propulsion, thereby increasing transit time of the substances, although it enhances contraction of the intestine.[3]

However, we found differing opinions in the literature on the gastrointestinal effects of bupivacaine and morphine co-administered via the epidural catheter. While Liu *et al.*[13] and de Leon-Casasola *et al.*[14] reported that its combination improved pain control compared with traditional methods using intravenous opioid, Hjortsø *et al.*[15] found little benefit in terms of intestinal motility when opioid and bupivacaine were used in combination. Epidural morphine has a negative effect on the recovery of intestinal motility.[16–19]

We found the time to the first postoperative passage of flatus and feces after surgery was reduced in the experimental group that was given the antagonist. We believe that the use of epidural naloxone antagonized the morphine-induced intestinal hypomotility and infer from this that the intestinal hypomotility from morphine is mediated by both central and systemic receptor level,[20] and that this mechanism can be prevented by epidural administration of naloxone.

As a morphine antagonist, naloxone acts directly on opioid receptors and is used to reverse clinical side-effects of opioid. However, titration of the dose is critical since it has differing effects at different doses.[21–23] The epidural administration of 0.208 $ug \cdot kg^{-1} \cdot hr^{-1}$ naloxone in our experiment was an effective and safe dose that maintained the analgesic effects of morphine and prevented one of morphine's side-effects - delayed recovery of intestinal motility.

We concluded that the intestinal hypomotility induced by epidural morphine can be reversed by epidural administration of 0.208 $ug \cdot kg^{-1} \cdot hr^{-1}$ naloxone without affecting its analgesic effects.

References

1 *Bonnet F, Vesinet C.* How can we improve the efficacy of morphine analgesia without increasing adverse effects? (French) Cah Anesthesiol 1994; 42: 191–4.

2 *Wattwil M, Thorén T, Hennerdal S, Garvill JE.* Epidural analgesia with bupivacaine reduces postoperative paralytic ileus after hysterectomy. Anesth Analg 1989; 68: 353–8.

3 *Thörn SE, Wattwil M, Näslund I.* Postoperative epidural morphine, but not epidural bupivacaine, delays gastric emptying on the first day after cholecystectomy. Reg Anesth 1992; 17: 91–4.

4 *Choi JH, Lee J, Choi JH, Bishop MJ.* Epidural naloxone reduces pruritus and nausea without affecting analgesia by epidural morphine in bupivacaine. Can J Anesth 2000; 47: 33–7.

5 *De Winter BY, Boeckxstaens GE, De Man JG, Moreels TG, Herman AG, Pelckmans PA.* Effects of mu- and kappa-opioid receptors on postoperative ileus in rats. Eur J Pharmacol 1997; 339: 63–7.

6 *Frame WT, Allison RH, Moir DD, Nimmo WS.* Effect of naloxone on gastric emptying during labour. Br J Anaesth 1984; 56: 263–6.

7 *Schang JC, Devroede G.* Beneficial effects of naloxone in a patient with intestinal pseudoobstruction. Am J Gastroenterol 1985; 80: 407–11.

8 *Dahl JB, Rosenberg J, Hansen BL, Hjortsø NC, Kehlet H.* Differential analgesic effects of low-dose epidural morphine and morphine-bupivacaine at rest and during mobilization after major abdominal surgery. Anesth Analg 1992; 74: 362–5.

9 *Glise H, Lindahl BO, Abrahamsson H.* Reflex adrenergic inhibition of gastric motility by nociceptive intestinal stimulation and peritoneal irritation in the cat. Scand J Gastroenterol 1980; 15: 673–81.

10 *Gillan MG, Pollock D.* Acute effects of morphine and opioid peptides on the motility and responses of the rat colon to electrical stimulation. Br J Pharmacol 1980; 68: 381–92.

11 *Porreca F, Filla A, Burks TF.* Spinal cord-mediated opiate effects on gastrointestinal transit in mice. Eur J Pharmacol 1983; 86: 135–6.

12 *Porreca F, Mosberg HI, Hurst R, Hruby VJ, Burks TF.* Roles of mu, delta and kappa opioid receptors in spinal and supraspinal mediation of gastrointestinal transit effects and hot-plate analgesia in the mouse. J Pharmacol Exp Ther 1984; 230: 341–8.

13 *Liu SS, Carpenter RL, Mackey DC, et al.* Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology 1995; 83: 757–65.

14 *de Leon-Casasola OA, Karabella D, Lema MJ.* Bowel function recovery after radical hysterectomies: thoracic epidural bupivacaine-morphine versus intravenous

patient-controlled analgesia with morphine: a pilot study. J Clin Anesth 1996; 8: 87–92.

15 *Hjortsø NC, Neumann P, Frosig F, et al.* A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. Acta Anaesthesiol Scand 1985; 29: 790–6.

16 *Thorén T, Wattwil M.* Effects on gastric emptying of thoracic epidural analgesia with morphine or bupivacaine. Anesth Analg 1988; 67: 687–94.

17 *Thorén T, Tanghöj H, Wattwil M, Järnerot G.* Epidural morphine delays gastric emptying and small intestinal transit in volunteers. Acta Anaesthesiol Scand 1989; 33: 174–80.

18 *Thörn SE, Wattwil M, Källander A.* Effects of epidural morphine and epidural bupivacaine on gastroduodenal motility during the fasted state and after food intake. Acta Anaesthesiol Scand 1994; 38: 57–62.

19 *Scheinin B, Asantila R, Orko R.* The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. Acta Anaesthesiol Scand 1987; 31: 161–4.

20 *Thorn SE, Wattwil M, Lindberg G, Sawe J.* Systemic and central effects of morphine on gastroduodenal motility. Acta Anaesthesiol Scand 1996; 40: 177–86.

21 *Frederickson RC, Burgis V, Edwards JD.* Hyperalgesia induced by naloxone follows diurnal rhythm in responsivity to painful stimuli. Science 1977; 198: 756–8.

22 *Jacob JJ, Tremblay EC, Colombel M-C.* Enhancement of nociceptive reactions by naloxone in mice and rats. (French) Psychopharmacologia 1974; 37: 217–23.

23 *Chesher GB, Chan B.* Footshock induced analgesia in mice: its reversal by naloxone and cross tolerance with morphine. Life Sci 1977; 21: 1569–74.