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ORIGINAL ARTICLE

Effects of epidural naloxone on pruritus induced by epidural morphine: a randomized controlled trial

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Background: Epidural morphine produces prolonged analgesia but has many side effects including pruritus. Naloxone is an antagonist that can reverse the side effects of morphine.
Method: We studied the effects of continuously administered epidural naloxone mixed with morphine on side effects and analgesia in a randomized, double blind, two-armed study. Fifty-eight pregnant women undergoing cesarean section were enrolled. All patients received a 4-mg epidural bolus of morphine in the post-anesthetic care unit. After this, patients in group M (n = 28) received continuous epidural morphine (6 mg over 48 h) in 0.1% bupivacaine; patients in group N (n = 30) received an epidural infusion containing naloxone (1.2 mg over 48 h) and morphine (6 mg over 48 h) in 0.1% bupivacaine. The infusion rate was 2 mL/h.
Results: The incidence (82% versus 47%) and severity of pruritus were lower in group N than group M ($P = 0.001$). There were no significant differences in pain score or in the incidence of nausea, vomiting or urinary disturbance between groups.
Conclusion: Continuous epidural infusion of naloxone combined with morphine is effective in reducing the incidence and severity of pruritus induced by epidural morphine.

Keywords: Epidural; Naloxone; Morphine; Pruritus

INTRODUCTION

Epidural morphine is used widely for pain relief because it has a prolonged analgesic effect,[1] but it produces many side effects such as pruritus, nausea, vomiting, respiratory depression and difficulty in micturition. To decrease its epidural side effects, many drugs have been tried,[2] such as naloxone,[3,4] nalbuphine,[4] dexamethasone,[5] droperidol,[6] anti-histamines and propofol.[3] The treatment of opioid-induced side effects remains a challenge. Pruritus is very common with epidural morphine, particularly among parturients.[6] Many patients who receive epidural morphine suffer from undesirable itching which requires treatment. Naloxone is a pure opioid antagonist that can reverse the side effects of morphine.[3,7] Kendrick et al.[4] and Gan et al.[8] reported that continuous intravenous infusion of naloxone was effective in decreasing epidural or intravenous morphine-induced pruritus. However, for this to be effective in those studies, another intravenous infusion device was required, separated from the infusion device for morphine. In our study, we mixed naloxone with morphine and infused them continuously through the epidural catheter using a single infusion device. Kakinohana et al.[9] reported that intrathecal naloxone had neuroprotective effects against morphine-potentiated motor dysfunction. We evaluated the ability of epidural naloxone to prevent the side effects of morphine, including pruritus, difficulty in micturition, nausea and vomiting after cesarean section.

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METHODS

Our Institutional Committee for Human Investigation approved this study and we obtained informed consent from each patient at the pre-anesthetic visit. Fifty-eight full-term pregnant women were enrolled in this study. All those included were to receive elective cesarean section under general anesthesia and had an ASA physical status of I or II. Exclusion criteria were histories of skin

allergy, gastrointestinal disease, urinary difficulty, drug abuse or psychiatric problems. We designed a double-blind, randomized, placebo-controlled study. All patients received routine monitoring including automatic measurement of blood pressure, electrocardiogram, continuous SaO_2 and end-tidal partial pressure of CO_2. For induction, each patient received propofol 2 mg/kg and succinylcholine 1 mg/kg i.v. Anesthesia was maintained with propofol 10 mg/kg/h^{-1}, vecuronium 4-mg bolus and 50% nitrous oxide in oxygen. After skin closure and before recovery from anesthesia, an epidural catheter was inserted for postoperative pain control in the right lateral decubitus position at interspaces L3/4 or L4/5.

After recovery in the post-anesthesia care unit, all patients received a 4-mg bolus of morphine in 10 mL of 0.8% lidocaine through the epidural catheter. To confirm successful siting of the epidural catheter, we checked for pain at rest and loss of sensation to pinprick. After this, patients were randomly assigned to one of two groups by computer-generated random number. Group M (n = 28) received continuous epidural morphine 6 mg in 96 mL of 0.1% of bupivacaine without naloxone. Group N (n = 30) received epidural preservative-free naloxone 1.2 mg (Samjin Pharm, Seoul) and morphine 6 mg in 96 mL of 0.1% of bupivacaine. The epidural infusion was continued at a rate of 2 mL/h (morphine 125 μg/h, naloxone 25 μg/h) with a continuous infusion device. The dose of naloxone that can reverse the pruritus of morphine was decided after a pilot study. These drug mixtures were prepared and connected randomly by an anesthetist who was not involved in this study.

Pruritus, nausea and pain were assessed during the first 24 h after epidural morphine and disturbance of micturition at 48 h, using subjective rating scores (Table 1). An investigator who was blind to treatment allocation assessed pain intensity at rest and on movement 24 h after surgery. Patients were asked whether they had suffered from pruritus, nausea or vomiting after surgery. If they said 'yes', its worst intensity was scored. Because the urinary catheter was routinely removed in the afternoon of the first postoperative day, scores of disturbance of micturition were obtained at 48 h after injection of morphine. If patients had intolerable pruritus or nausea, an anti-histamine drug or metoclopramide was administrated i.v.

Sample size was determined using the SigmaStat for Windows version 2.0 (SPSS inc.) based on the data in the studies by Sanansilp et al.[6] and Saiah et al.[3] In the former study, the incidence of pruritus following epidural morphine was 70%[6] and in the latter, i.v. naloxone produced an 80% reduction of pruritus overall.[3] Therefore, with $\alpha = 0.05$ and $\beta = 0.20$, the estimated sample size was 25 patients in each group. SPSS version 10.0 (SPSS inc.) was used for statistical analysis. The incidence was analyzed using χ^2 test or Fisher's exact test and severity of variables using likelihood ratio χ^2 test. Age and body weight of patients were analyzed using *t*-tests. For all cases, $P < 0.05$ was considered statistically significant.

Table 1. Rating scores for pruritus, nausea, disturbance of micturition and pain

Variables	Score	Description
Pruritus	1	No itching
	2	Mild localized itching
	3	Mild generalized itching
	4	Moderate itching
	5	Intolerable severe itching and treatment required
Nausea	1	No nausea
	2	Mild nausea
	3	Moderate nausea
	4	Intolerable severe nausea and treatment required
Disturbance of micturition	1	No problem
	2	Voiding difficult initially but with a normal volume
	3	Voiding difficult with a reduced volume
	4	Voiding impossible and re-catheterization required
Pain	1	No pain or uterine contraction pain only
	2	Pain only with strenuous movement (e.g. getting down from the bed)
	3	Pain with light movement (ward ambulation)
	4	Pain during bed rest

RESULTS

The demographic data for both groups are listed in Table 2. There were no significant differences in age or body weight between groups.

During the first postoperative day, the incidence of pruritus was lower in group N than group M; group M: 23/28 (82%), group N: 14/30 (47%) ($P = 0.003$). Fig. 1 shows the distribution of pruritus scores. Group M had more severe itching than group N ($P = 0.001$). Most patients (97%) in group N had no or mild pruritus, only one had moderate itching and none had severe itching. Thirteen patients (46%) in group M had moderate or severe pruritus and 4 (14%) required treatment.

Table 2. Demographic data

	Group M (n = 28)	Group N (n = 30)
Age (years)	28.4 ± 3.2	29.6 ± 3.8
Body weight (kg)	71.1 ± 9.6	70.3 ± 8.1

Values are expressed as mean ± standard deviation.
Group M received epidural morphine. Group N received epidural morphine plus naloxone.