British Journal of Anaesthesia **99 (2):** 270–5 (2007)
doi:10.1093/bja/aem146 Advance Access publication June 7, 2007

BJA

Epidural naloxone reduces postoperative nausea and vomiting in patients receiving epidural sufentanil for postoperative analgesia

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Background. Epidural opioids have excellent analgesic properties, but their side-effects limit their use in patient-controlled epidural analgesia. This study was designed to evaluate the effect of epidural naloxone on the side-effects of sufentanil, focusing on postoperative nausea and vomiting (PONV) in patients undergoing total knee replacement (TKR).

Methods. After obtaining Institutional Review Board approval and informed consent, 50 patients undergoing unilateral TKR were randomly assigned to receive either sufentanil in ropivacaine alone (Group C, n=25) or the same solution with naloxone (Group N, n=25) for their postoperative epidural analgesia. Episodes of PONV and five-point-scaled nausea scores were evaluated at 6, 12, and 24 h after epidural analgesia was started. Visual analogue scale (VAS) score for pain and the incidence of sedation, pruritus, hypotension, and respiratory depression were also evaluated at each of three time points.

Results. The nausea score in Group N was significantly lower than that in Group C. The VAS pain score at rest and on movement were significantly lower in Group N than in Group C at 24 h. Other opioid-induced side-effects were not significantly different.

Conclusions. Epidural naloxone was effective in reducing PONV induced by epidural sufentanil and additionally enhanced the analgesic effect. Therefore, concomitant infusion of a small dose of epidural naloxone should be considered to reduce PONV, especially in patients at greater risk for PONV.

Br J Anaesth 2007; **99**: 270–5

Keywords: analgesic techniques, extradural; analgesics opioid, sufentanil; antagonists opioid, naloxone; PONV

Accepted for publication: April 20, 2007

Total knee replacement (TKR) is associated with severe postoperative pain and adequate pain relief is essential in the postoperative period.[1 2] An epidural infusion of a local anaesthetic–narcotic mixture is a common modality for pain relief after TKR,[3] and epidural morphine is widely used.[4] However, it has been associated with respiratory depression, postoperative pruritus, and postoperative nausea and vomiting (PONV). The reported incidences of postoperative pruritus and PONV vary from 8.5% to 90%, and from 34% to 70%, respectively, in patients receiving epidural morphine.[5–8] Sufentanil, a highly lipophilic opioid, is used instead of morphine because epidural sufentanil may produce analgesia primarily by a spinal mechanism when combined with local anaesthetics.[9] Epidural sufentanil, when compared with morphine, has been associated with a lower incidence of delayed respiratory depression.[10] However, the incidence of PONV has remained high in patients administered epidural sufentanil.[11–13]

Previous studies reported that small doses of the opioid antagonist naloxone administered i.v. and epidurally allow maintenance of analgesia while reducing morphine-related side-effects such as pruritus, nausea, and intestinal hypomotility.[14–16] This study was designed to evaluate the

effect of epidural naloxone on the side-effects of sufentanil, focusing on PONV in patients undergoing TKR.

Methods

After obtaining approval of the Institutional Review Board and written informed consent, 50 adult patients with ASA physical status I–II undergoing primary, unilateral TKR were included. Patients were excluded from the study if they had contraindications to neuraxial anaesthesia, allergy to study drugs, chronic opioid use, significant myocardial, renal, or hepatic impairment, or nausea and vomiting during the operation. Subjects were then allocated to one of the two treatment groups in the post-anaesthesia care unit and received either sufentanil in ropivacaine (Group C, n=25) or sufentanil in ropivacaine with naloxone (Group N, n=25) for their postoperative epidural analgesia. Group assignment was randomized using a sealed envelope system. Both patients and anaesthesia providers were blinded with respect to study group allocation throughout the study period. An independent researcher prepared the study solutions. The study solution of Group C consisted of ropivacaine 0.2% and sufentanil 1.0 $\mu g\ ml^{-1}$ and the study solution of Group N consisted of ropivacaine 0.2% and sufentanil 1.0 $\mu g\ ml^{-1}$ with preservative-free naloxone. The amount of naloxone, which was based on patient's body weight, in 1 ml of the study solution of Group N was 0.0333 $\mu g\ kg^{-1}$. The basal rate of the patient-controlled analgesia (PCA) device was set at 6 ml h^{-1} and the bolus dose was set 0.5 ml with a 15 min lockout period, which made the maximum infusion rate to be 8 ml h^{-1}. Therefore, the infusion range of naloxone was 0.20–0.27 $\mu g\ kg^{-1}\ h^{-1}$. Before surgery, patients were instructed on the use of the PCA device and the visual analogue scale (VAS) score for pain assessment.

Patients were placed in a left lateral decubitus position for a combined spinal-epidural procedure. After local anaesthesia of the skin at the L3–4 or L4–5 interspace, an 18-gauge Tuohy needle (Portex, NH, USA) was introduced via a midline approach into the epidural space using a loss of resistance technique. A 27-gauge Whitacre tip spinal needle was then placed through the Tuohy needle, and subarachnoid placement was confirmed by the free flow of cerebrospinal fluid (CSF). All patients received isobaric tetracaine 0.5%, 2 ml (Pantocainsterile, Daihan pharm., Seoul, Korea) with 1:1000 epinephrine 0.1 ml. The spinal needle was removed and a 20-gauge, closed end, multiport catheter (Portex, NH, USA) was inserted 4–5 cm cephalad within the epidural space, and the patient was placed in a supine position. Electrocardiogram and arterial oxygen saturation were monitored continuously and blood pressure was recorded non-invasively every 5 min until the end of the surgical procedure, and then every 10 min until recovery. If the arterial blood pressure of the patient decreased by more than 20% from baseline, then 300–500 ml of colloids and incremental boluses of i.v. ephedrine (4–6 mg) were used. Scores for pain, sensory block level, intensity of motor block, nausea, sedation, pruritus, respiratory depression, and hypotension were recorded at 20 min after the spinal anaesthesia. Pain was scored on a 100 mm VAS (0=no pain, 100=the worst pain imagined). The sensory block level was assessed at the maximal level of cold sensation at the midclavicular line using an alcohol swab bilaterally. The intensity of motor block was evaluated with the Bromage scale (1=no motor block, 2=knee blocked and mobility of ankle preserved, 3=mobility of ankle difficult, and 4=knee and ankle blocked). A ventilatory frequency $\leq$8 bpm was defined as respiratory depression, and a decrease in mean arterial blood pressure more than 20% from the basal value was defined as hypotension.

When patients arrived at the post-anaesthesia care unit, a physician blinded to the treatment group assessed initial sensory block level, which was assessed at the maximal level of cold sensation at the midclavicular line using an alcohol swab bilaterally. The sensory block level was then checked at 10 min intervals until regression of the sensory level below T10. When regression of the sensory level was below the T10 dermatome, epidural analgesia was started using the PCA technique with an electronic infusion pump (WalkMed® PCA, McKinley, CO, USA) containing the study solution by a physician blinded to the treatment group. The infusion pump setting included a 6 ml h^{-1} continuous infusion and a 0.5 ml bolus dose with a 15 min lockout period for 24 h after operation. Patients with a VAS pain score higher than 50 were given meperidine 25 mg i.m. as rescue analgesia. Patients with a nausea score higher than 3 were given ondansetron 4–6 mg i.v. Each patient was interviewed at 6, 12, and 24 h after the start of epidural PCA administration. At these time points, episodes of PONV and nausea score were recorded. Nausea was defined as the subjective sensation of a desire to vomit without any expulsive muscular movements. Vomiting was defined as expulsive efforts followed by elimination of gastric content. The nausea score was categorized as 1=no nausea, 2=mild nausea, treatment is not necessary, 3=moderate nausea, treatment may be desirable, but patient can tolerate it, 4=severe nausea and treatment is necessary, 5=intractable nausea, patient complains despite treatment.[17] Pain intensity was assessed at rest and on movement using the VAS. In addition, upper level of cold sensation, intensity of motor block, somnolence, pruritus, and respiratory depression were recorded. Urinary retention could not be assessed at 6 or 12 h because all patients had an indwelling urinary catheter at 12 h after operation.

Sample size was based on the power analysis from a similar epidural PCA study,[17] which adopted this 0.7 nausea score difference, an α risk of 0.05 and a β risk of 0.2 (SigmaStat 3.1, Systat Software, Inc., CA, USA). Statistical analysis was performed using the Statistical

Package for Social Sciences software (SPSS 12.0 for windows, SPSS Inc., IL, USA). Results are expressed as mean (SD), mean (range), median (inter-quartile range), or a number of patients. χ^2 tests, independent *t*-tests, and Mann–Whitney *U*-test were used to compare variables between the groups where appropriate. The VAS scores between groups were analysed with repeated measures of analysis of variance (ANOVA) followed by Bonferroni-corrected *post hoc* analysis. A *P*-value of less than 0.05 was considered statistically significant.

Results

Fifty patients completed the study protocol. Patient characteristics excluding body weight were comparable between the two groups. The duration of surgery and the history of PONV and motion sickness were comparable between the two groups. The maximal levels of sensory block at 20 min after spinal anaesthesia were also similar (Table 1).

The VAS pain scores at rest and on movement were significantly lower in Group N than in Group C at 24 h (P=0.001 and 0.013, respectively) (Figs 1 and 2). There were no differences in total infused volume of analgesic regimen and supplemental analgesic use between the two groups (Table 2).

Nausea scores were significantly lower in Group N than in Group C at 6 and 12 h after PCA was started (P<0.05) (Table 3). The use of anti-emetic agents was significantly lower in Group N than in Group C at 6, 12, and 24 h (P< 0.05) (Table 3).

There were no significant differences in pruritus or sedation between the two groups (Table 4).

No patients in either group had respiratory depression and hypotension.

No patients in either group had urinary retention at 24 h.

Discussion

The results of this study indicate that the concomitant epidural infusion of sufentanil and naloxone for postoperative

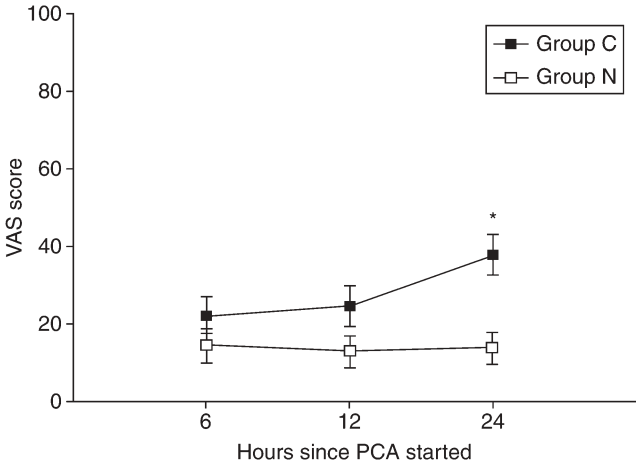

Fig 1 Mean VAS pain scores at rest. Mean VAS pain scores at 6, 12, and 24 h after the infusion of PCA regimens were lower in Group N, but only the difference in the VAS pain score at 24 h was statistically significant. Values are mean (SD). *Significantly different compared with Group C (P=0.001).

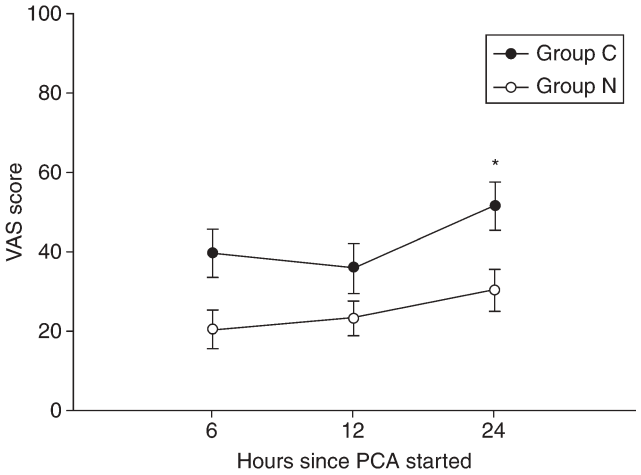

Fig 2 Mean VAS pain scores on movement. Mean VAS pain scores on movement at 6, 12, and 24 h after the infusion of PCA regimens were lower in Group N, but only the difference in the VAS pain score at 24 h was statistically significant. Values are mean (SD). *Significantly different compared with Group C (P=0.013).

Table 1 Patients' characteristic, past history, and duration of surgery. Weight, height, BMI, and duration of surgery values are given as mean (SD), age as mean (range), history of PONV and motion sickness as the number of patients (%) and maximal sensory block as median (inter-quartile range). BMI, body mass index; PONV, postoperative nausea and vomiting. *Significantly different compared with Group C (P<0.05)

	Group C (n=25)	Group N (n=25)
Sex (M/F)	3/22	4/21
Age (yr)	66.9 (53–74)	66.3 (55–75)
Height (cm)	152.6 (6.1)	154.6 (6.9)
Weight (kg)	61.2 (8.7)	66.3 (9.1)*
BMI (kg m^{-2})	26.3 (3.4)	27.8 (4.0)
History of PONV	5 (20)	6 (24)
History of motion sickness	4 (16)	2 (8)
Maximal sensory block	T6 (T6–T8)	T6 (T6–T8)
Duration of surgery (min)	84.9 (9.1)	86.2 (17.1)

Table 2 Total infused volume of analgesic regimen (TIVAR) during 0–6, 6–12, 12–24 h and patients requiring i.m. meperidine 25 mg at 6, 12, and 24 h after the infusion of PCA regimens. Values of TIVAR are means (SD) and those for i.m. meperidine are the number of patients (%). PCA, patient-controlled analgesia

	Group C (n=25)	Group N (n=25)
TIVAR (ml)		
0–6 h	37.9 (3.7)	37.7 (4.5)
6–12 h	40.1 (9.6)	39.7 (5.8)
12–24 h	74.3 (4.8)	73.4 (5.5)
I.M. meperidine		
6 h	5 (20)	3 (12)
12 h	7 (28)	3 (12)
24 h	13 (52)	9 (36)

Table 3 Incidence of PONV, nausea score, and patients requiring anti-emetics at 6, 12, and 24 h after the infusion of PCA regimens. Values are number of patients (%). PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting. [a]Nausea score was categorized as 1=no nausea, 2=mild nausea, treatment is not necessary, 3=moderate nausea, treatment may be desirable, but patient can tolerate it, 4=severe nausea and treatment is necessary, 5=intractable nausea, patient complains despite treatment. *Significantly different compared with Group C ($P<0.05$)

	Group C ($n=25$)	Group N ($n=25$)
No. of patients having episodes of PONV (%)		
6 h	13 (52)	7 (28)
12 h	10 (40)	5 (20)
24 h	10 (40)	6 (24)
Nausea score[a] (1/2/3/4/5)		
6 h	12/4/4/5/0	18/5/2/0/0*
12 h	15/1/4/5/0	20/4/1/0/0*
24 h	15/4/5/1/0	19/4/2/0/0
Anti-emetic use		
6 h	13 (52)	4 (16)*
12 h	7 (28)	1 (4)*
24 h	7 (28)	1 (4)*

Table 4 Incidence of pruritus and sedation at 6, 12, and 24 h after the infusion of PCA regimens. Values are number of patients (%). PCA, patient-controlled analgesia

	Group C	Group N
Pruritus		
6 h	2 (8)	0
12 h	1 (4)	0
24 h	4 (16)	0
Sedation		
6 h	1 (4)	3 (12)
12 h	2 (8)	2 (8)
24 h	1 (4)	1 (4)

analgesia not only reduces the incidence and severity of PONV but also enhances the analgesic effect of sufentanil. Although overall VAS pain scores were lower in Group N, only the difference in the VAS pain score at 24 h was statistically significant.

Epidural administration of opioids combined with local anaesthetic is a popular method in perioperative analgesia because of its synergistic effect. However, opioid-induced side-effects such as nausea and vomiting, pruritus, respiratory depression, and urinary retention limit the use of opioids in postoperative pain control because these side-effects can be more distressing and debilitating than the pain itself. In particular, PONV is a major concern in opioid analgesia because patients rated PONV as the most undesirable side-effect and indicated that avoidance of PONV was of a higher priority than avoidance of postoperative pain.[18] The most commonly identified risk factors for PONV include female gender, non-smoking status, history of PONV or motion sickness, extended duration of anaesthesia, postoperative opioid use, and age.[19 20] Roberts and colleagues[21] reported that both postoperative opioid use and female gender significantly influenced PONV, whereas opioid use, in particular, had a dose-dependent relationship with PONV. In studies that included both male and female patients receiving epidural analgesia, the overall mean incidence of nausea was 18.8% (14.0–24.8%), and vomiting occurred in 16.2% (12.5–20.7%). The incidence of nausea and vomiting was higher in studies that included only female patients, 39.1% (26.3–53.7%) and 30.2% (24.3–36.9%), respectively.[22]

There have been many trials aimed at reducing the side-effects of neuraxial opioids. Some of these studies investigated the use of lipophilic opioids instead of hydrophilic opioids such as morphine. Sufentanil, a lipophilic opioid, offers some unique advantages due to its greater lipophilicity and μ-receptor-binding capacity. Whether epidurally administered sufentanil acts spinally or supraspinally via systemic absorption remains controversial. However, a series of studies of epidural sufentanil infusion after thoracotomy demonstrated that the concentration of epidural sufentanil was higher in CSF than in plasma and that sufentanil was highly localized within the CSF to the level of administration after both single bolus administration and infusion.[23 24] Joris and colleagues[9] also proved that in combination with epidural local anaesthetic, sufentanil requirements were less epidurally than i.v., suggesting that epidural sufentanil produces analgesia primarily by a spinal mechanism when combined with local anaesthetic. Studies exploring the side-effects of epidural sufentanil have not shown consistent results. However, in most studies using epidural sufentanil, the incidence of PONV was higher than that of other side-effects.[11–13 23] In this study, no patients receiving epidural sufentanil in ropivacaine without naloxone had serious side-effects related to neuraxial opioids other than PONV. The second most common opioid-related side-effect in these patients was pruritus (8–16%) but only one patient (4%) required treatment.

Another avenue in decreasing the side-effects of epidural opioids is the concurrent use of low-dose naloxone i.v. or epidurally.[14–16 25] I.V. infusion of naloxone at 0.25 $\mu g\,kg^{-1}\,h^{-1}$ has been effective in reducing and reversing morphine-related side-effects without affecting analgesia or even paradoxically enhancing morphine's analgesic potency.[14 25] However, since i.v. infusion of naloxone requires another infusion device separate from the epidural device in patients receiving epidural analgesia for postoperative pain control, naloxone was mixed with epidural morphine in local anaesthetics in two previous human studies.[15 16] This continuous naloxone infusion reduced pruritus, nausea, and intestinal hypomotility without affecting analgesia. In animal studies, the safety of neuraxial naloxone and its neuroprotective effect has been proved.[26 27] Cole and colleagues[26] reported that with a 1.0 $mg\,kg^{-1}$ intrathecal dose of naloxone, there was no histological evidence of spinal cord toxicity or behavioural and physiological perturbations in the rat. Furthermore, they have demonstrated a protective effect of intrathecal naloxone against spinal cord injury.

It is better to infuse naloxone continuously because it has a half-life of 55 min and therefore intermittent administration will result in the fluctuation of naloxone concentration.[28] Other studies on naloxone used either a continuous or intermittent technique.[15 16 28] In addition to continuous infusion, an intermittent bolus dose of naloxone was also given at the same time as the opioid solution was triggered by the PCA pump because naloxone was mixed with the opioid solution in this study. This method of administration may have further reduced side-effects because the ratio of the blood concentrations of sufentanil and naloxone was maintained constant throughout the study period.

The concentration of naloxone used in this study was based on that used in other studies, which ranged from 0.167 $\mu g\ kg^{-1}\ h^{-1}$ to 0.412 $\mu g\ kg^{-1}\ h^{-1}$ in patients receiving epidural morphine.[15–17] Among patients receiving naloxone, the mean (SD) dosage received over 24 h was 0.21 (0.01) $\mu g\ kg^{-1}\ h^{-1}$. The mean (SD) dosage of naloxone received over the first 6 h was 0.21 (0.03) $\mu g\ kg^{-1}\ h^{-1}$, over the second 6 h 0.22 (0.03) $\mu g\ kg^{-1}\ h^{-1}$, and for the last 12 h 0.20 (0.01) $\mu g\ kg^{-1}\ h^{-1}$.

In this study, no patients receiving epidural sufentanil in ropivacaine had any serious side-effects except PONV, regardless of whether they received naloxone coadministration. PONV was markedly reduced in patients receiving a concomitant infusion of naloxone. Furthermore, both nausea scores and anti-emetic use were significantly lower in these patients. Considering that the majority of patients receiving epidural naloxone were female, the incidence of PONV was lower than that seen in other studies.[22] A low dose of epidural naloxone not only reduced PONV but also improved the VAS pain score at 24 h in Group N. The potential mechanisms for these effects of low doses of naloxone include: (1) low-dose naloxone may enhance release of endogenous opioid peptides by blocking presynaptic autoinhibition of enkephalin release[29] and (2) low-dose naloxone directly and competitively antagonizes the Gs protein-coupled excitatory opioid receptors that are responsible for the hyperalgesia occasionally reported with opioid administration without attenuating inhibitory Gi/Go-coupled opioid receptors mediating analgesia.[30]

There are several limitations to this study. First, we used i.m. meperidine as rescue analgesia because the orthopaedic surgeon was unwilling to use a non-steroidal anti-inflammatory drug due to its negative effect on bone healing. Although there were no differences in the incidence and severity of PONV between patients with and without meperidine in this study, the use of another opioid may have influenced the incidence of PONV. Secondly, the naloxone dose used was weight-based but that of sufentanil and ropivacaine was not. This was in line with other studies on opioids and local anaesthetics, in which the continuous infusion rate and bolus dose in adults were not weight-based. On the other hand, studies on epidural naloxone were all weight-based doses, and since there was no other reference dose, a weight-based dose was used.[15–17]

In conclusion, epidural naloxone was effective in reducing PONV induced by epidural sufentanil and additionally enhances the analgesic effect. Therefore, concomitant infusion of a small dose of naloxone should be considered to reduce PONV, especially in patients at greater risk for PONV.

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