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Effects of Prophylactic Nalmefene on the Incidence of Morphine-related Side Effects in Patients Receiving Intravenous Patient-controlled Analgesia

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Background: **Opioid-related side effects associated with intravenous patient-controlled analgesia can be reduced by a low-dose naloxone infusion. The influence of nalmefene, a pure opioid antagonist with a longer duration of action, on opioid-related side effects has not been evaluated. This study was designed to determine the dose–response relation for nalmefene for the prevention of morphine-related side effects in patients receiving intravenous patient-controlled analgesia.**

Methods: **One hundred twenty women undergoing lower abdominal surgery were enrolled in the study. General anesthesia was induced using thiopental and rocuronium and maintained with desflurane, nitrous oxide, and fentanyl or sufentanil. All patients received neostigmine and glycopyrrolate to reverse residual neuromuscular blockade. No prophylactic antiemetics were administered. At the end of surgery, patients were randomized to receive saline, 15 μg nalmefene, or 25 μg nalmefene intravenously. The need for antiemetic and antipruritic drugs and the total consumption of morphine during the 24-h study were recorded. The incidences of postoperative nausea, vomiting, pruritus, and pain were recorded 30 min after patients were admitted to the postanesthesia care unit. In addition, patient remembrance of these side effects was noted at 24 h after operation.**

Results: **The need for antiemetic and antipruritic medications during the 24-h study period was significantly lower in the patients receiving nalmefene compared with those receiving placebo. However, the need to treat side effects was similar in the two nalmefene groups. Prophylactic administration of nalmefene reduced the patients remembrance of nausea and itching as assessed 24 h after operation. Although the total consumption of morphine during the 24-h study period was similar in the three groups, retrospectively patients who received nalmefene characterized their pain as less severe in the previous 24 h.**

Conclusion: **Compared with placebo, prophylactic administration of nalmefene significantly decreased the need for antiemetics and antipruritic medications in patients receiving intravenous patient-controlled analgesia with morphine. (Key words: Analgesics; antagonists; nausea; opioids; postoperative complications; pruritus; vomiting.)**

INTRAVENOUS patient-controlled analgesia (IV-PCA) is one of the most commonly used techniques to manage postoperative pain. However, patients using an IV-PCA system may experience opioid-related side effects, including nausea, vomiting, and pruritus. Various drugs have been used as boluses or infusions to prevent these opioid-related side effects.[1] However, the effectiveness of these drugs is controversial. A recent study reported a significant reduction in morphine-related side effects using an infusion of naloxone in conjunction with morphine administered by an IV-PCA system.[2] Nalmefene, a new pure μ-receptor antagonist, is a water-soluble naltrexone derivative with a longer duration of action than naloxone.[3–6] The mean terminal β elimination half-life of nalmefene is 8.5 h, compared with 1 h for naloxone.[4] The hypothesis of this study was that prophylactic administration of intravenous nalmefene could decrease the incidence of morphine-related side effects in patients using IV-PCA.

This randomized, double-blind, placebo-controlled study was designed to determine the dose–response of nalmefene for preventing morphine-related side effects in patients receiving IV-PCA. In addition, the effect of nalmefene on the overall quality of analgesia was also evaluated.

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Materials and Methods

After we received institutional review board approval, we enrolled 120 consenting women (classified as American Society of Anesthesiologists physical status I, II, or III) who were scheduled for lower abdominal surgery. Patients with significant cardiovascular, pulmonary, renal, or hepatic dysfunction, and those with a history of allergy to opioids or their antagonists and a history of drug or alcohol dependence were excluded from the study. All patients were given instructions regarding the use of the PCA system.

After premedication with 2 mg intravenous midazolam, general anesthesia was induced with 3–5 mg/kg intravenous thiopental, and tracheal intubation was facilitated using 0.6 mg/kg intravenous rocuronium. Anesthesia was maintained with desflurane (3 or 4%) in a mixture of 60% nitrous oxide in oxygen and intermittent bolus doses of fentanyl or sufentanil. Heart rate, arterial blood pressure (noninvasive), pulse oximetry, temperature, end-tidal carbon dioxide, and end-tidal desflurane concentrations were monitored. No prophylactic antiemetic agents were administered. At the end of the surgery, all patients received neostigmine, 50 μg/kg, and 10 μg/kg intravenous glycopyrrolate to antagonize neuromuscular blockade. When spontaneous breathing resumed, 1 or 2 mg intravenous morphine was administered, as necessary, to achieve a respiratory rate of 12–15 breaths/min. At the conclusion of the surgery, patients were assigned randomly, using a computer-generated random-number sequence, to receive saline (group 1), 15 μg nalmefene (group 2), or 25 μg nalmefene (group 3) intravenously. A blinded person who was not involved in data collection administered the study drug.

In the postanesthesia care unit (PACU), patients who reported pain received morphine (2–5 mg intravenously every 5 min) until they were pain free. After this "loading dose," IV-PCA morphine was started. Patients could self-administer 3 mg morphine (the demand dose) every 10 min (the lockout interval). If analgesia was inadequate, the lockout time was decreased or a background infusion of 0.5–1 mg/h morphine was started, or both. The total dose of morphine used during the 24-h study was recorded.

The episodes of nausea or vomiting and the need for treatment were recorded by a blinded observer 30 min after the patients arrived in the PACU. The severity of pain was assessed, 30 min after arrival in the PACU, using a four-point categoric scale (0 = none, 1 = slightly uncomfortable, 2 = moderate but tolerable, 3 = severe and intolerable). Rescue medications for nausea, vomiting, or both were administered if nausea lasted for more than 15 min or if at any time the patients requested them. The rescue medications for nausea and vomiting consisted of 0.625–1 mg droperidol, 4 mg ondansetron, or 5–10 mg prochlorperazine given intravenously. Rescue medication for pruritus was 25–50 mg diphenhydramine given intravenously. The need for antiemetic and antipruritic medications during the 24-h study period was recorded. In addition, patient recollection of nausea, vomiting, or itching in the previous 24 h was noted. Furthermore, a 10-cm visual analog scale was used to assess retrospectively the overall severity of pain (0 and 10 labeled as "no pain" and "worst pain imaginable") and the overall pain relief (0 and 10 labeled as "no pain relief" and "complete pain relief") at 24 h.

An SAS computer package (SAS Institute, Cary, NC) was used for all statistical analyses. For the purpose of analysis, for patients receiving fentanyl, the total amount of fentanyl used was converted to analgesic equivalents of sufentanil (1 μg sufentanil equivalent to 10 μg fentanyl). Continuous variables (*e.g.,* demographic data, duration of anesthesia, and intraoperative and postoperative opioid use) were analyzed using an analysis of variance test with Bonferroni correction for *post hoc* comparisons. Frequency distributions were determined for each of the nonparametric outcome measurements (*e.g.,* nausea, vomiting, pruritus, pain) by group. Treatment groups were compared using chi-square contingency table analysis and likelihood ratio chi squares. If the overall likelihood ratio chi-square was significant, the overall chi-square was partitioned to evaluate pairwise differences between groups.[7] A P value less than 0.05 was considered significant.

Results

One hundred twenty patients participated in the study, with 40 patients enrolled in each of three groups. One patient in group 2 was excluded from the statistical analyses because of protocol violation. There were no significant differences among the groups with respect to age, weight, height, duration of anesthesia, and use of intraoperative opioids (table 1).

There were no significant differences between the groups in the number of patients reporting nausea and vomiting and the need for antiemetic treatment in the PACU (table 2). Although there was no difference in the overall incidence of pain among the groups, a signifi-

Table 1. Demographic Data and Intraoperative Opioid Requirements in the Three Treatment Groups

	Placebo	Nalmefene 15 μg	Nalmefene 25 μg
Number (n)	40	39	40
Age (yr)	44 ± 11	42 ± 9	41 ± 10
Weight (kg)	84 ± 20	80 ± 21	78 ± 20
Height (cm)	161 ± 7	163 ± 8	159 ± 8
Type of surgery			
Abdominal hysterectomy (n)	34	36	36
Other (adnexal mass removal) (n)	6	3	4
Duration of anesthesia (min)	166 ± 71	147 ± 56	137 ± 54
Intraoperative sufentanil (μg)	69 ± 30	71 ± 32	63 ± 33
Intraoperative morphine (mg)	12 ± 4	11 ± 4	13 ± 6

Values are mean ± SD.

cantly more patients receiving nalmefene 25 μg reported severe pain in the PACU (table 2).

The need for antiemetic and antipruritic medications during the 24-h study period was significantly less in the patients receiving nalmefene compared with those receiving placebo (table 3). However, there was no difference between the nalmefene groups. Significantly more patients in the placebo group recalled being nauseated and remembered reporting itching compared with the patients in the nalmefene groups (table 3). There was no difference in the number of patients who remembered vomiting during the 24-h study period (table 3). Although the total consumption of morphine during the 24-h study period was similar in the three groups, the overall 24-h pain scores were significantly less in the patients receiving nalmefene (table 3). In addition, the overall 24-h pain relief scores were significantly greater in patients receiving nalmefene compared with those receiving placebo.

Discussion

The incidence of postoperative nausea and vomiting (PONV) is predictably high with the use of opioids. Interestingly, most patients consider PONV to be more distressing and debilitating than pain.[8] Indeed, PONV was cited by 71% of patients as the reason for the poor rating they gave their perioperative experiences.[9] In addition to reducing patient satisfaction, PONV may delay recovery and increase the duration of hospital stay. In a study evaluating morphine-related side effects in patients receiving placebo, 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone, or 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone in conjunction with IV-PCA, the incidences of nausea were 80, 45, and 35%, respectively.[2] Semple *et al.*[10] reported PONV in as many as 88% of patients receiving IV-PCA with morphine after abdominal hysterectomy. Similarly, Gan *et al.*[11] reported the incidence of PONV with IV-PCA with morphine as much as 80% without administration of prophylactic antiemetic agents.

In this study, the prophylactic administration of nalmefene significantly reduced the need for antiemetics during the 24-h study period. However, the absence of antiemetic effects of nalmefene in the PACU may be related to the timing of the administration of nalmefene. It is possible that if nalmefene had been administered 15–30 min before the end of surgery, the incidence of nausea in the PACU may have been reduced. Several studies have evaluated the antiemetic effectiveness of droperidol, promethazine, or metoclopramide added to IV-PCA morphine.[1] However, these drugs have a minimal effect on PONV. In addition, they may be associated with side effects. Increased sedation and extrapyramidal reactions have been reported as late as 24 h after small doses of droperidol were given.[12] Furthermore, the addition of antiemetic drugs to morphine or the use of a naloxone infusion increases the complexity of IV-PCA therapy.

The addition of droperidol to morphine PCA after a prophylactic dose at induction has been shown to reduce the degree of nausea and the incidence of requests for rescue antiemetic, but it also increases the degree of sedation.[13] In contrast, the addition of droperidol (5 mg) in PCA morphine (30 mg) after a single dose of droperidol (1.25 mg) at the end of surgery resulted in a greater degree of sedation but did not improve the antiemetic

Table 2. The Incidence and Need for Treatment of Nausea, Vomiting, and Pain in the Postanesthesia Care Unit in the Three Treatment Groups

	Placebo	Nalmefene 15 μg	Nalmefene 25 μg
Nausea	21 (52.5)	17 (43.6)	15 (37.5)
Vomiting	3 (7.5)	2 (5.1)	5 (12.5)
Pain			
None	11 (27.5)	14 (35.9)	12 (30.0)
Mild	10 (25.0)	6 (15.4)	1 (2.5)
Moderate	5 (12.5)	8 (20.5)	5 (12.5)
Severe	14 (35.0)	11 (28.2)	22 (55.0)*
Loading dose of morphine (mg)	8 ± 3	8 ± 5	7 ± 3
Antiemetic therapy	10 (25.0)	10 (25.6)	13 (32.5)

Values are numbers (percentages) or mean ± SD.

* $P < 0.05$ *versus* other groups.

Table 3. The Need for Treatment of Nausea, Vomiting, and Pain over the 24-h Study Period and the 24-h Patient Assessments in the Three Treatment Groups

	Placebo	Nalmefene 15 μg	Nalmefene 25 μg
Treatment of side effects			
Antiemetic therapy	25 (62.5)	13 (33.3)*	13 (32.5)
Antipruritic therapy	9 (22.5)	2 (5.1)*	2 (5.0)*
Total (24 h) morphine dose (mg)	50 ± 25	45 ± 24	56 ± 26
24-h patient assessments			
Recalled being nauseated	33 (82.5)	19 (48.7)*	17 (42.5)*
Remembered vomiting	3 (7.5)	4 (10.3)	6 (15.0)
Remembered complaining of itching	24 (60.0)	2 (5.1)*	2 (5.0)*
Pain severity VAS (cm)	5.5 ± 2.9	3.5 ± 2.4*	2.3 ± 2.5*
Pain relief VAS (cm)	6 ± 3	8 ± 2*	9 ± 2*

Values are numbers (percentages) or mean ± SD.

VAS = visual analog score.

* $P < 0.05$ *versus* placebo group.

effect.[11] A recent study showed that the simultaneous titration of promethazine (0.625 mg/PCA dose, an average of 17.6 mg/24 h) and morphine decreased nausea associated with PCA therapy.[14] The addition of metoclopramide (0.5 mg/ml) to morphine reduced the incidence of severe PONV during the first 6 h, but the overall incidence of PONV was not affected.[15] Use of transdermal hyoscine with PCA morphine reduced the incidence of PONV only minimally (from 88% to 78%).[10]

The incidence of pruritus in patients receiving IV-PCA morphine after abdominal hysterectomy was reported to be 55%, compared with 20–25% in patients receiving a naloxone infusion in conjunction with IV-PCA.[2] In a study of women undergoing cesarean section, the incidence of pruritus while they received IV-PCA was 60%; however, only 5% of these patients required treatment.[16] In a similar patient population, Harrison *et al.*[17] reported a 35% incidence of pruritus, with 11% of patients requiring treatment. In this study, nearly 23% of patients in the placebo group needed antipruritic treatment, and prophylactic administration of nalmefene significantly decreased the need for treatment to 5%.

The patients in the three groups self-administered similar doses of morphine during the 24-h study period. However, the patients receiving nalmefene characterized their pain retrospectively as less severe in the previous 24 h (*i.e.*, lower pain scores and higher pain relief scores) than did those who received placebo. This supports the observations by previous investigators that the end point chosen by patients using IV-PCA opioids is not necessarily total pain relief, but rather a balance between analgesia and the side effect profile.[18] It is also suggested that, frequently, pain and itching are closely associated. Therefore, the higher incidence of pruritus in the placebo group may have resulted in the higher pain scores.[19]

Several investigators reported an analgesic effect of low-dose naloxone.[2,20] It is possible that low doses of nalmefene may also have some analgesic effects. In contrast to the findings in this study, Gan *et al.*[2] observed no difference in the pain scores in patients receiving placebo or naloxone infusion; however, morphine use was significantly less in the patients receiving low-dose naloxone infusion compared with those receiving placebo. The 24 h assessment may have represented the severity of pain at that specific time rather than the overall degree of pain during the previous 24 h. However, this element of bias should have been similar in the three study groups. Nevertheless, more data collection time points would have better clarified the effects of nalmefene on the intensity of postoperative pain.

Until recently, naloxone was the only pure opioid antagonist available. Its onset of action after intravenous administration is rapid (1 or 2 min), but its duration of action is relatively short (30–60 min). Therefore, it must be administered as an infusion to achieve a prolonged effect. In a placebo-controlled study, Gal and DiFazio[4] reported that nalmefene could antagonize the analgesia and respiratory depression associated with opioid administration during a prolonged period of time. In addition, increasing the dose of nalmefene was effective in further prolonging its duration of action. Konieczko *et al.*[5] reported similar conclusions using 0.4 mg nalmefene given intravenously. These authors also reported that nalmefene was four times more potent than naloxone at the μ- and κ-opioid receptors.[5] However, Glass *et al.*[6] reported that nalmefene is equipotent to naloxone but had a longer duration of action after a single intravenous

dose. The doses of nalmefene (15 and 25 μg) used in this study were chosen based on the findings of previous reports with naloxone (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$)[2] and assume that nalmefene is as potent as naloxone.

Although high doses of nalmefene have been used safely,[3,21] administration of 75 μg nalmefene to reverse postoperative respiratory depression has been reported to cause acute pulmonary edema.[22] The other possible side effects associated with opioid antagonists include recurrence of postoperative pain, tachycardia, hypertension, dizziness, headache, nausea, and vomiting. Therefore, nalmefene should be used with caution in patients with significant cardiovascular dysfunction. The initial recommended dose to reverse postoperative opioid-related respiratory depression is 0.1 μg/kg, with a maximum dose of 1 μg/kg.[23] Use of higher doses is likely to increase the incidence and severity of side effects.

In conclusion, in patients receiving IV-PCA with morphine, prophylactic administration of nalmefene decreased the need for antiemetic and antipruritic medications without affecting the quality of analgesia.

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References

1. Woodhouse A, Mather LE: Nausea and vomiting in the postoperative patient-controlled analgesia environment. Anaesthesia 1997; 52: 770–5

2. Gan TJ, Ginsberg B, Glass PSA, Fortney J, Jhaveri R, Perno R: Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. ANESTHESIOLOGY 1997; 87:1075–81

3. Dixon R, Howes, J Gentile J, Hsu H-B, Hsiao J, Garg D, Weidler D, Meyer M, Tuttle R: Nalmefene: Intravenous safety and kinetics of a new opioid antagonist. Clin Pharmacol Ther 1986; 39:49–53

4. Gal TJ, DiFazio CA: Prolonged antagonism of opioid action with intravenous nalmefene in man. ANESTHESIOLOGY 1986; 64:175–80

5. Konieczko KM, Jones JG, Barrowcliffe MP, Jordan C, Altman DG: Antagonism of morphine-induced respiratory depression with nalmefene. Br J Anaesth 1988; 61:318–23

6. Glass PSA, Jhaveri RM, Smith R: Comparison of potency and duration of action of nalmefene and naloxone. Anesth Analg 1994; 78:536–41

7. Zar J: Biostatistical Analysis, 3rd Edition. Upper Saddle River, NJ, Prentice-Hall, 1996, pp 483–503

8. Watcha MF, White PF: Postoperative nausea and vomiting. Its etiology, treatment, and prevention. ANESTHESIOLOGY 1992; 77:162–84

9. Madej TH, Simpson KH: Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following major gynaecological surgery. Br J Anaesth 1986; 58: 884–7

10. Semple P, Madej TH, Wheatley RG, Jackson IJB, Stevens J: Transdermal hyoscine with patient-controlled analgesia. Anaesthesia 1992; 47:399–401

11. Gan TJ, Alexander R, Fennelly M, Rubin AP: Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of postoperative nausea and vomiting. Anesth Analg 1995; 80:81–5

12. Melnick BM: Extrapyramidal reactions to low-dose droperidol. ANESTHESIOLOGY 1988; 69:424–6

13. Williams OA, Clarke FL, Harris RW, Smith P, Peacock JE: Addition of droperidol to patient-controlled analgesia: Effect on nausea and vomiting. Anaesthesia 1993; 48:881–4

14. Silverman DG, Freillich J, Sevarino FB, Paige D, Preble L, O'Connor TZ: Influence of promethazine on symptom-therapy scores for nausea during patient-controlled analgesia with morphine. Anesth Analg 1992; 74:735–8

15. Walder AD, Aitkenhead AR: Antiemetic efficacy of metoclopramide when included in a patient-controlled analgesia infusion. Anaesthesia 1994; 49:804–6

16. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: A comparison with epidural and intramuscular narcotics. ANESTHESIOLOGY 1988; 68:444–8

17. Harrison DM, Sinatra R, Morgese L, Chung JH: Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. ANESTHESIOLOGY 1988; 68:454–7

18. Chumbley GM, Hall GM, Salmon P: Patient-controlled analgesia: An assessment by 200 patients. Anaesthesia 1998; 53:216–21

19. Ballantyne JC, Loach AB, Carr DB: Itching after epidural and spinal opiates. Pain 1988; 33:149–60

20. Levine JD, Gordon NC, Fields HL: Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. Nature 1979; 278:740–1

21. Kaplan JL, Marx JA: Effectiveness and safety of intravenous nalmefene for emergency department patients with suspected narcotic overdose: A pilot study. Ann Emerg Med 1993; 22:187–90

22. Henderson CA, Reynolds JE: Acute pulmonary edema in a young male after intravenous nalmefene. Anesth Analg 1997; 84:218–9

23. Abramowicz M: Nalmefene—A long acting injectable opioid antagonist. Med Lett Drugs Ther 1995; 37:97–8