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Opioid-sparing Effects of a Low-dose Infusion of Naloxone in Patient-administered Morphine Sulfate

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Background: **A naloxone infusion is effective in reducing epidural and intrathecal opioid–related side effects. The use of naloxone infusion concomitant with intravenous morphine patient-controlled analgesia (PCA) has not been evaluated, probably because of an expected direct antagonism of the systemic opioid effect. The authors compared the incidence of morphine-related side effects and the quality of analgesia from two small doses of naloxone infusion.**

Methods: **Sixty patients classified as American Society of Anesthesiologists physical status 1, 2, or 3 who were scheduled for total abdominal hysterectomies were enrolled in the study. Patients received a standardized general anesthetic. In the postanesthetic care unit, patients received morphine as a PCA. They were randomized to receive either 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone (low dose), 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (high dose), or saline (placebo) as a continuous infusion. Verbal rating scores for pain, nausea, vomiting, and pruritus; sedation scores; requests for antiemetic; and morphine use were recorded for 24 h. Blood pressure, respiratory rate, and oxyhemoglobin saturation were also monitored.**

Results: **Sixty patients completed the study. Both naloxone doses were equally effective in reducing the incidence of nausea, vomiting, and pruritus compared with placebo ($P < 0.05$ by the chi-squared test). There was no difference in the verbal rating scores for pain between the groups. The cumulative morphine use was the lowest in the low-dose group (42.3 ± 24.1 mg; means ± SD) compared with the placebo (59.1 ± 27.4 mg) and high-dose groups (64.7 ± 33.0 mg) at 24 h ($P < 0.05$ by analysis of variance). There was no incidence of respiratory depression (<8 breaths/min) and no difference in sedation scores, antiemetic use, respiratory rate, and hemodynamic parameters among the groups.**

Conclusions: **Naloxone is effective in preventing PCA opioid–related side effects. Naloxone infusion at 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ not only attenuates these side effects but appears to reduce postoperative (beyond 4–8 h) opioid requirements. This dosing regimen can be prepared with 400 μg naloxone in 1,000 ml crystalloid given in 24 h to a patient weighing 70 kg. (Key words: Analgesia: patient-controlled; postoperative. Analgesics, opioid: morphine. Antagonist, opioid: naloxone. Anesthetic technique: general. Complications, postoperative: nausea; vomiting; pruritus.)**

THE treatment of acute postoperative pain by patient-controlled analgesia (PCA) and by epidural and spinal opioids has gained widespread acceptance and is now standard practice in many hospitals. However, opioids are associated with side effects such as nausea and vomiting, pruritus, urinary retention, and respiratory depression. Naloxone is a pure μ-receptor antagonist and is effective in reducing and reversing opioid-related side effects. Various authors have studied the influence of naloxone infusion on postoperative analgesia and respiratory depression after epidural[1,2] and intrathecal[3] opioids. However, there are no published data on continuous infusion of naloxone in patients receiving morphine PCA with the aim of reducing opioid-related side effects. The purpose of this study was to compare the incidence of morphine-related side effects and the quality of analgesia in three groups of patients: those given two small doses of naloxone and those given placebo.

Materials and Methods

We enrolled 60 patients classified as American Society of Anesthesiologists physical status 1, 2, or 3 who were scheduled for total abdominal hysterectomies under general anesthesia after we obtained institutional review board approval and written informed patient con-

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Table 1. Demographic Data

	Placebo (n = 20)	Low Dose (n = 20)	High Dose (n = 20)
Age (yr)	51 ± 14	47 ± 12	50 ± 13
Weight (kg)	71.3 ± 16.6	71.3 ± 20.6	72.2 ± 18.5
Duration of surgery (min)	217.6 ± 59.9	211.3 ± 94.9	193 ± 96.6
Intraoperative fentanyl (μg)	592.1 ± 226.8	491.6 ± 207.2	554.0 ± 234

Values are mean ± SD.

Table 2. Incidence of Nausea, Vomiting, Rescue Antiemetic Use, and Pruritus

	Placebo (n = 20) [n (%)]	Low Dose (n = 20) [n (%)]	High Dose (n = 20) [n (%)]	*P* Value*
Nausea	16 (80)	9 (45)	7 (35)	0.01
Vomiting	11 (55)	4 (20)	4 (20)	0.02
Rescue antiemetic	13 (65)	8 (40)	6 (30)	NS
Pruritus	11 (55)	5 (25)	4 (20)	0.04

NS = not significant.

* Low or high dose groups *versus* placebo.

sent. Before the surgery, patients were taught how to use the PCA system and were told that they could request rescue antiemetic or antipruritic treatment when required. All patients received 1 - 2 mg midazolam intravenously as premedication. General anesthesia was induced with 3 - 5 mg/kg thiopental and 2 μg/kg fentanyl and maintained with 66% nitrous oxide, 0.5 - 1.5% isoflurane in oxygen, and $\leq 3\ \mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl. All patients received 0.1 mg/kg vecuronium intravenously to facilitate endotracheal intubation and incremental doses for subsequent neuromuscular blockade during surgery. At the end of surgery, 40 μg/kg neostigmine and 8 μg/kg glycopyrrolate were administered to antagonize neuromuscular blockade. In the recovery room, patients were attached to a PCA machine (Lifecare 5500 PCA; Abbott Laboratories, Chicago, IL) containing 30 mg morphine sulfate in 30 ml 0.9% saline (1 mg/ml). The following settings were established: a loading dose of 40 μg/kg was repeated to achieve patient comfort; a maintenance dose was 20 μg/kg; and a lockout interval was 8 min with no preset maximum dose. Patients were randomly assigned to one of three groups using computer-generated random numbers concealed in envelopes. The low-dose group received 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone, the high dose group received naloxone 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and the placebo group received 0.9% saline as a continuous infusion. The study solutions were prepared by the pharmacist and diluted in saline to produce equal volumes to ensure proper blinding. A preset infusion rate of 10 ml/h was commenced at the same time as the initiation of PCA. Verbal

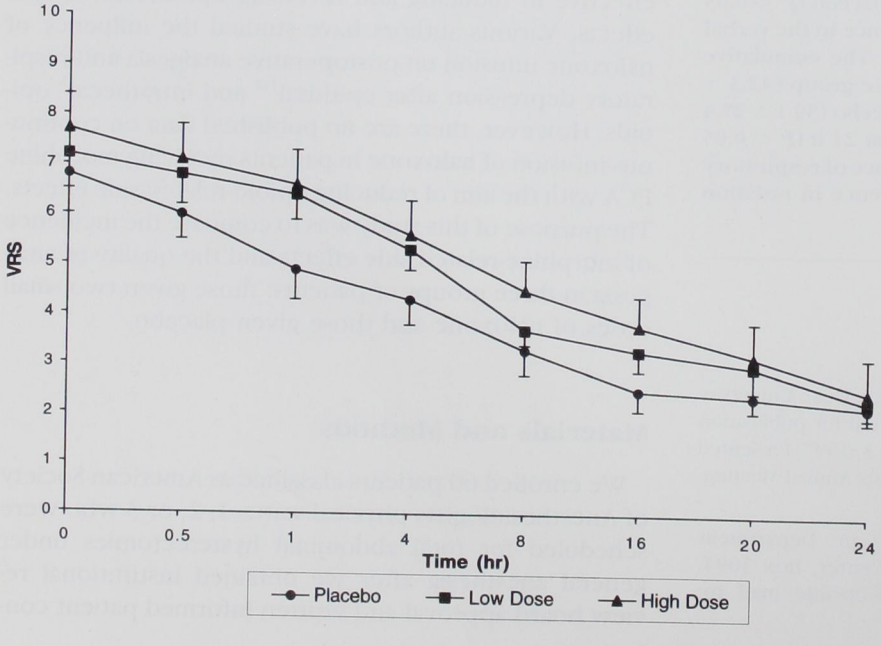

Fig. 1. Verbal rating scores for pain at rest plotted *versus* time (means ± SEM).

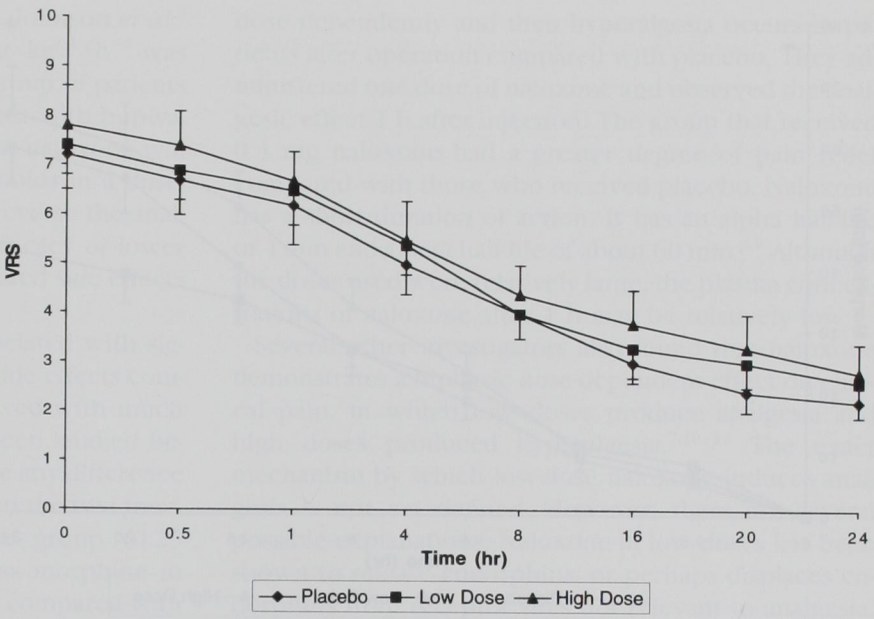

Fig. 2. Verbal rating scores for pain during activity plotted *versus* time (means ± SEM).

rating scores for pain at rest and with activity (coughing and deep inspiration) of 0–10; Ramsay sedation scores[4] of 1–6; side effects, such as nausea, vomiting, pruritus, and respiratory depression; and requests for antiemetic (12.5 mg promethazine at the patient's request) and morphine were recorded by an independent research nurse at 0, 0.5, 1, 4, 8, 16, 20, and 24 h. All patients remained in the study for the entire study period. Blood pressure, respiratory rate, and oxyhemoglobin saturation were also monitored. Continuous outcomes were analyzed by analysis of variance with Tukey's *post hoc* comparisons in which a significant overall group difference was found, and repeated measures analysis of variance (verbal rating pain scores). Nominal outcomes were analyzed using the chi-squared test. Probability values <0.05 were considered significant. For sample size calculation, 18 patients in each group would give at least 80% power to detect a group difference of 50% in the incidence of nausea and vomiting from 60% to 30% with an alpha coefficient of 0.05. Results are presented as means ± SD or means ± SEM (for figures).

Results

All 60 patients completed the study. There were no differences in the demographic data among the groups (table 1). The incidence of nausea in the placebo, low-dose, and high-dose groups were 80%, 45%, and 35%, respectively ($P = 0.01$ by the chi-squared test). The incidence of vomiting was 55% in the placebo group and 20% each in the low- and high-dose groups ($P = 0.02$ by the chi-squared test). The incidence of pruritus was also higher in the placebo group, at 55%, compared with the low-dose (25%) and the high-dose groups (20%) ($P = 0.04$ by the chi-squared test). Naloxone-treated groups appeared to have fewer requests for rescue antiemetic compared with the placebo group. However, the difference was not significant (table 2). There was no difference in the verbal rating scores for pain at rest (figure 1) or with activity (figure 2) during the study period among the three groups. Cumulative morphine use at 24 h was the least in the low-dose group (42.3 ± 24.1 mg) compared with the placebo (59.1 ± 27.4 mg) and high-dose groups (64.7 ± 33 mg); $P < 0.05$ by analysis of variance (figure 3). However, these differences only began to be apparent after 4–8 h. There were no incidences of respiratory depression (<8/min) and no difference in respiratory rate (figure 4), sedation scores, blood pressure, heart rate, and oxygen saturation among the groups.

Discussion

Morphine delivered by the PCA system is effective in relieving pain relief after surgery.[5] However, it is

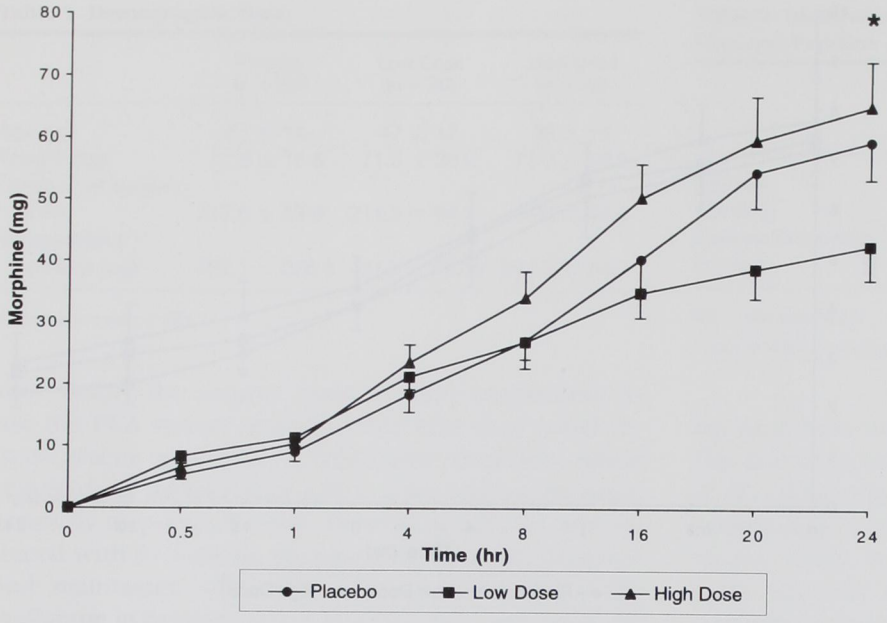

Fig. 3. The cumulative morphine dose plotted *versus* time (means ± SEM). *$P < 0.05$ for low-dose plotted *versus* placebo or high-dose regimens.

associated with opioid-related side effects such as nausea and vomiting, pruritus, respiratory depression, and urinary retention. Naloxone has been shown to be effective against these side effects.[1–3] This was confirmed in the present study. The doses that we used were based on findings from previous investigations. Two previous studies examined the effects of naloxone on analgesia and respiratory depression after epidural fentanyl[2] and morphine.[1] They showed that 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone given intravenously was associated with a reduction

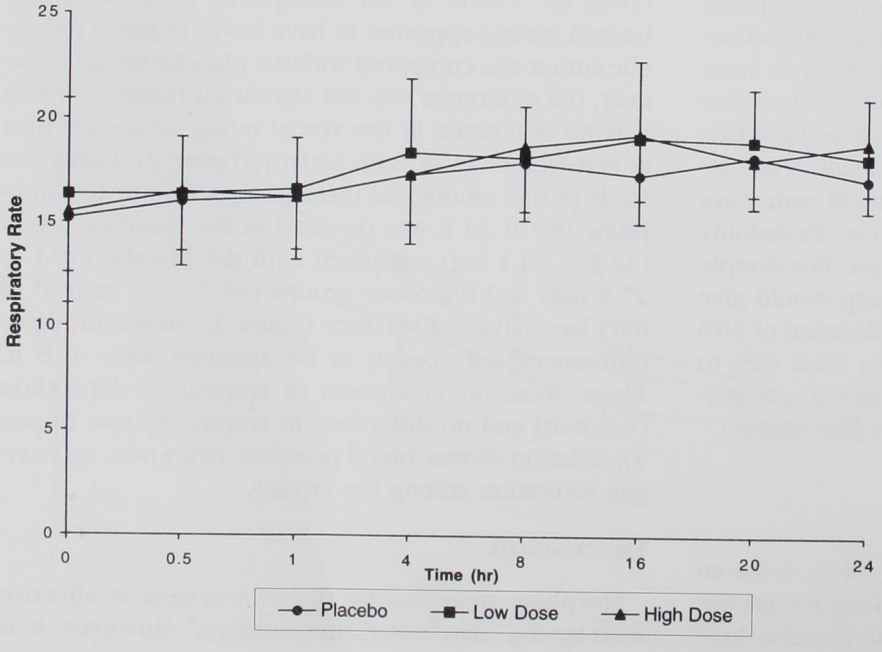

Fig. 4. Respiratory rate plotted *versus* time (means ± SEM).

in the duration and quality of analgesia. Johnson *et al.*[3] showed that a naloxone infusion >1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was associated with inferior analgesia in a group of patients having hip surgery under spinal analgesia with bupivacaine and morphine. Thus it is clear that naloxone will reverse the systemic side effects of opioids in a dose-dependent manner. Higher doses will reverse the analgesia. Thus we wanted to assess the efficacy of lower doses of naloxone to prevent opioid-related side effects without antagonizing analgesia.

The two treatment groups were associated with significant reduction in morphine-related side effects compared with placebo. These were achieved with much smaller doses of naloxone than have been studied before. In addition, there did not seem to be any difference in the effectiveness of naloxone between the two treatment groups. However, the low-dose group (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$) required significantly less morphine in 24 h and achieved comparable analgesia compared with the other groups. The high-dose group had greater morphine requirements compared with placebo, although the difference was not statistically significant. Wright *et al.*[6] found that naloxone at 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (similar to the high-dose group in this study) attenuated the pain relief provided by intrathecal morphine in a group of patients having lumbar laminectomy.

Our study produced two noteworthy findings: first, a marked reduction in opioid-related side effects without an increase in verbal rating pain score; and second, an actual opioid-sparing effect of 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone. Opioid-related side effects are probably prevented because each of the opioid effects observed have different concentration-response curves. If the analgesic concentration response is far to the right of the other opioid effects (*i.e.*, the concentrations to provide analgesia are higher than those that produce opioid-related side effects such as nausea, vomiting, and pruritus), then a low dose of an antagonist will reverse their effects without influencing the analgesic concentration response. However, this does not explain the surprising and intriguing opioid-sparing effect seen with low-dose naloxone. Thus some other mechanisms must be responsible.

Indeed there is evidence to suggest that naloxone has a dose-dependent pain response in both animal and human species. In a rat model, Woolf[7] noted that small doses of naloxone produced paradoxical analgesia, whereas larger doses resulted in hyperalgesia. Levine *et al.*[11,12] found that naloxone initially produces analgesia dose dependently and then hyperalgesia occurs in patients after operation compared with placebo. They administered one dose of naloxone and observed the analgesic effect 1 h after injection. The group that received 0.4 mg naloxone had a greater degree of pain relief compared with those who received placebo. Naloxone has a short duration of action. It has an alpha half-life of 4 min and a beta half-life of about 60 min.[8,9] Although the doses used were relatively large, the plasma concentrations of naloxone after 1 h may be relatively low.

Several other investigators also found that naloxone demonstrates a biphasic dose-dependent effect on clinical pain, in which low doses produce analgesia and high doses produced hyperalgesia.[7,10-13] The exact mechanism by which low-dose naloxone induces analgesia is not yet defined. However, there are several possible explanations. Naloxone in low doses has been shown to release endorphins, or perhaps displaces endorphins from receptor sites not relevant to analgesia, whereas at higher doses it blocks the action of the released or displaced endorphin at the postsynaptic receptor for analgesia. The time course of these binding experiments was approximately 1 h.[14]

Similarly, Ueda *et al.*[10] found that very low doses of naloxone (a 1-μg/kg subcutaneous injection) produced significant analgesia in mice. Kurashi *et al.*[15] found that pain induced the release of Metenkephalin from the nucleus reticularis gigantocellularis, one of the most sensitive areas of opioid analgesia in the brain. Enkephalin release has been shown to be governed by a presynaptic regulatory system; that is, large quantities of enkephalin result in a negative feedback, reducing further release. It was postulated that a very small dose of naloxone may act by inhibiting the presynaptic autoinhibition of enkephalin release by endogenous enkephalin itself.[10] Thus, at this dose, naloxone may act presynaptically rather than postsynaptically. This finding corresponds well with data obtained in experiments with norepinephrine or dopamine neurotransmission.[16,17] Furthermore, the finding that the dose region in which naloxone shows potent analgesia is low and narrow also corresponds with data obtained in experiments of enkephalin release. The naloxone-induced analgesia was evident at 30 min when a small dose of naloxone was injected intracisternally, and similar analgesic effects were observed at a later time (not specified) when it was administered subcutaneously.[10]

The cumulative doses of morphine used in our study only became apparent after more than 4-8 h. This may

be due to the fact that morphine doses in the initial phase were rather small and thus indistinguishable among the groups, or it may be due to the time course for naloxone to be effective in displacing endorphins from nonanalgesic receptors, demonstrating the phenomenon just described. There is also evidence to suggest that opioid-related side effects such as nausea, vomiting, and pruritus may be mediated by presynaptic receptors.[18–20] This may be an alternative explanation for the prevention of opioid-related side effects without increasing pain when using a low-dose naloxone infusion ($<1\ \mu g \cdot kg^{-1} \cdot h^{-1}$).

It is also possible that continuous infusion of naloxone potentiated the activity of opioid receptors, which is an up-regulation phenomenon. Two previous studies have shown a twofold increase in analgesic potency of opioids with μ receptor agonist activity after a prolonged (7 days) naloxone infusion in animals.[21,22] Up-regulation of opioid receptors within 24 h of naloxone infusion has not been studied. However, up- and down-regulation of β receptors have been demonstrated within 30 min during and after cardiopulmonary bypass.[23] It is plausible that the density of opioid receptors may be up-regulated after a low-dose naloxone infusion.

We did not find any differences in the respiratory rate among the three groups. In another study in which naloxone was used at higher infusion rates, at 5 and 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$, a significant increase in respiratory rates occurred compared with participants given placebo.[1] Our study suggests that smaller doses of naloxone do not increase respiratory rates. We did not study the incidence of postoperative urinary retention because most of the patients had a urinary catheter inserted before the surgical procedure.

Results from this study suggest that low-dose naloxone given as a continuous infusion concomitant with the administration of morphine sulfate is likely to be useful in clinical practice. The dose regimen that we used ($0.25\ \mu g \cdot kg^{-1} \cdot h^{-1}$) can be prepared with 400 μg (1 ampule) naloxone in 1,000 ml crystalloid given to a 70-kg patient in 24 h. The addition of naloxone directly into morphine PCA is chemically and physically compatible.[6] Use of longer-acting direct opioid antagonists such as nalmefene, which is equipotent to naloxone,[9] in intermittent doses may be as effective and warrant further investigations. Our findings also give us further insight into the mechanism of opioid-induced side effects. The conventional understanding of naloxone acting as a direct postsynaptic opioid antagonist may be flawed. Further studies need to be performed to establish the mechanism of naloxone-induced analgesia.

In summary, small doses of naloxone infused at 0.25 or 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ are equally effective in reducing PCA opioid-related side effects. Naloxone at 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ has the additional advantage of providing opioid-sparing effects.

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