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Low-dose naloxone does not improve morphine-induced nausea, vomiting, or pruritus☆

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Abstract

Objective: We tested the hypothesis that low-dose naloxone delivered with intravenous (IV) bolus morphine to emergency department patients in pain would reduce nausea.

Methods: Randomized, double-blind, placebo-controlled trial. Patients receiving 0.10 mg/kg morphine IV bolus rated pain, nausea, and pruritus on 100-mm visual analog scales at enrollment and 20 minutes. Patients were randomized to 0.25 μg/kg naloxone or equal volume placebo administered with IV morphine.

Results: One hundred thirty-one enrolled, 99 (76%) treated according to protocol with sufficient data for analysis. At 20 minutes the difference between groups (naloxone-placebo) was 1 mm (95% CI [confidence interval], −9 to 11) for nausea, 1 mm (95% CI, −3 to 3) for pruritus, 4% (95% CI, −1 to 9) for vomiting, and 0% (95% CI, −5 to 5) for rescue antiemetics. Pain was significantly reduced in both groups.

Conclusion: Addition of 0.25 μg/kg naloxone to bolus morphine does not improve nausea, pruritus, vomiting, or reduce use of rescue antiemetics when administered to emergency department patients in pain.

1. Introduction

Adequate pain treatment has been recognized as an important and often neglected part of emergency department (ED) care [1,2]. Opioid medications effectively treat pain, but are associated with unwanted side effects, including nausea, vomiting, and pruritus. These adverse effects may limit acceptance of opioid drugs by both patients and caregivers [3,4].

Naloxone is a μ-receptor antagonist. Low doses of this drug (at least 100-fold lower than doses used to reverse opioid-induced respiratory depression) have been shown to reduce nausea, vomiting, and pruritus when administered by the intrathecal, epidural, and patient-controlled analgesia

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(PCA) intravenous (IV) routes [5-7]. Naloxone may limit opioid side effects by acting on a set of neural Gs-coupled excitatory opioid receptors. This same mechanism has been found in the laboratory to enhance morphine's antinociceptive potency and may be clinically important in the treatment of pain [8-13].

The utility of a low-dose opioid antagonist in enhancing analgesia and limiting the adverse effects of IV bolus morphine has not been previously studied. Emergency department practitioners often administer morphine by IV bolus because this route is rapid, reliable, and well suited to the ED. We tested the primary hypothesis that low-dose naloxone administered with bolus IV morphine to ED patients in pain would reduce morphine-associated nausea. We also examined low-dose naloxone's effect on pain, vomiting, pruritus, and use of rescue antiemetics.

2. Methods

2.1. Study design

Prospective, randomized, double-blind, placebo-controlled trial, conducted at 2 university-affiliated urban hospital emergency departments.

2.2. Study setting and population

All adult patients (>20 years old at one hospital, >18 years old at the other) receiving morphine IV for the treatment of acute pain were eligible for enrollment. Patients unable to complete a visual analog scale (VAS) and those with morphine or naloxone allergy were excluded. The study was approved by the institutional review boards of both institutions. Written consent was obtained from all enrolled patients.

2.3. Study protocol

An allocation schedule was prepared by a research pharmacist using a computerized routine (http://randomization.com) to randomly assign an equal number of patients to each of 2 groups. The treatment group received 0.10 mg/kg morphine bolus with 0.25 μg/kg naloxone. The control group received 0.10 mg/kg morphine with an equal volume of normal saline placebo. The study drug was premixed by the pharmacist to produce a naloxone concentration of 2.5 μg/mL. Both solutions were placed in identical-appearing numbered vials, thus blinding both patients and caregivers. Upon receiving an order for morphine for a patient enrolled in the study, a nurse who had been previously instructed in the protocol prepared 0.10 mg/kg of morphine sulfate and 0.10 mL/kg of the solution from the next consecutively numbered study vial. The allocation list was in the sole possession of the research pharmacist throughout the study. Opaque tamper-proof envelopes with group assignment information were available to the caregivers to be opened in a medical emergency. There were no instances in which the code was broken.

2.4. Measurements

Before administration of morphine and the study drug or placebo, patients were presented with three 100-mm visual analog scales: a pain scale, a nausea scale, and a pruritus scale. These scales each consist of a 10-cm horizontal line, anchored on the left with "no pain," "no nausea" or "no itching" and on the right end with "worst possible pain," "worst possible nausea" or "worst possible itching." The pain and nausea scales have been previously validated [14-19], the pruritus scale has not. Patients were asked to make a mark with a pencil along each 10-cm line at the spot that best represented their discomfort. After a 20-minute interval, patients were again asked to rate their pain, nausea, and pruritus on the VAS without access to prior scores. The incidence of vomiting in both groups and use of rescue antiemetics were also recorded. Demographic data, as well as information on use of opioid medication at home and within the 6 hours before enrollment, were gathered.

2.5. Statistical methods

2.5.1. Sample size

We determined that 29 patients in each group (total N = 58) would be needed to detect a difference of at least 35% between the 2 groups in the proportion of patients experiencing the primary end point of nausea, at a 2-tailed significance level (α) of .05, with a power of 80%. Similarly, 29 (total N = 58), 41 (total N = 82), and 62 (total N = 124) patients in each group would be required to detect a difference of at least 35%, 30%, and 25% between the 2 groups in the proportion of patients experiencing the secondary end points of vomiting, pruritus, and need for rescue antiemetics, respectively. The proportions used in the calculation of sample size were based on previously reported differences in the frequency of nausea (35%), vomiting (35%), pruritus (30%), and need for rescue antiemetics (25%) among postoperative patients treated with and without low-dose naloxone [5]. The sample size calculations were performed with NQuery Advisor, Release 5.0 (Saugus, Mass).

2.5.2. Data analysis

The demographic characteristics of the 2 groups and their initial values on the symptom scales are presented as means with standard deviations and simple proportions. Changes in nausea, pruritus, and pain were calculated by subtracting the 20-minute values from the baseline values (time 0) on each scale. Changes in symptom scale VAS scores measuring pain, nausea, and pruritus, and differences in these scores between the 2 groups under comparison are expressed as means with 95% confidence intervals (95% CI). Differences between the 2 groups in occurrence of vomiting and use of rescue antiemetics are expressed as proportions with 95%

CIs. Statistical analysis was performed using SPSS ver 10.0.7 (Chicago, Ill).

3. Results

Of the 131 patients enrolled, sufficient data were available for analysis on 122. Of these, 23 patients received doses of morphine that were lower than the dose specified in the protocol. Data from these patients (9 in the naloxone group and 14 in the control group) were excluded from further analysis. Data analysis was performed on the remaining 99 patients (see CONSORT schematic, Fig. 1, [20]).

The baseline characteristics of the 99 patients in the final sample were similar in the 2 groups under comparison (Table 1). Both groups had high initial levels of pain as indicated by mean VAS scores above 80 mm. Although both groups experienced statistically and clinically significant reductions in pain associated with morphine administration, the *difference* in pain reduction between the 2 groups was neither clinically nor statistically significant [19]. As shown in Table 2, the difference in change in pain between the naloxone vs placebo groups averaged −5 mm (95% CI, −17 to 7), that is, the naloxone group had a slightly greater reduction in pain on the VAS that was neither statistically nor clinically significant.

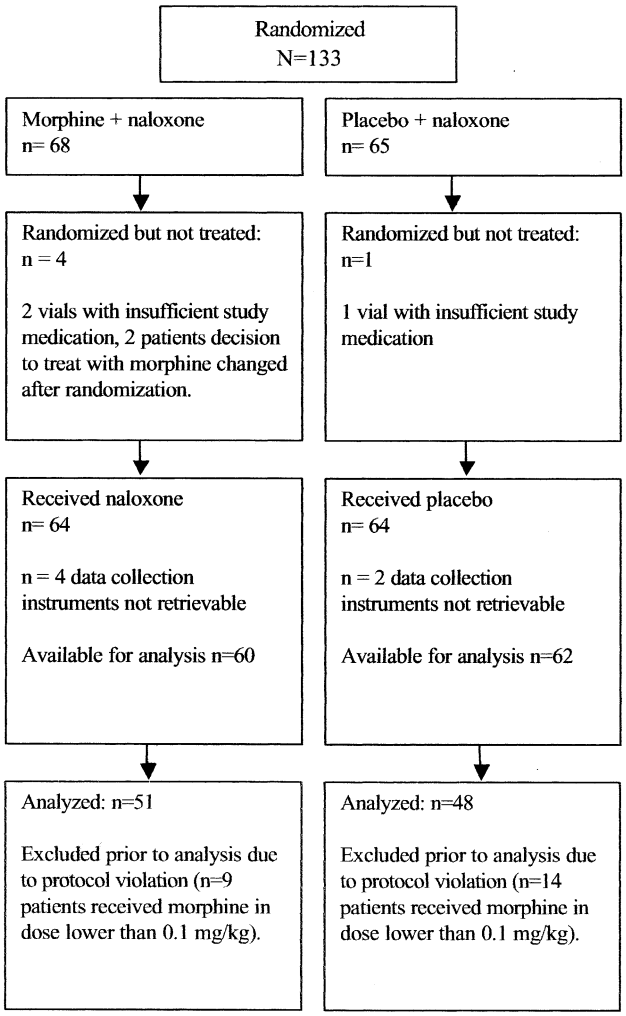

Fig. 1 CONSORT flow diagram.

Table 1 Baseline features of patients by group allocation

	Morphine + naloxone (N = 51)	Morphine + saline (N = 48)
Age (y; mean ± SD)	44 ± 13	43 ± 14
Sex (female; %)	49	50
Initial pain (mm; mean ± SD)	87 ± 19	81 ± 18
Initial nausea (mm; mean ± SD)	23 ± 31	24 ± 32
Initial pruritus (mm; mean ± SD)	03 ± 06	02 ± 04
Use of opioids within 6 h before enrollment (%)	10 (20)	7 (15)
Home use of opioids, N (%)	8 (16)	6 (13)

There were no statistically significant differences between the naloxone and placebo groups in reduction of the primary end point of nausea (1 mm; 95% CI, −9 to 11; nor in the secondary end points of pruritus (1 mm; 95% CI, −3 to 3), or vomiting (4%; 95% CI, −1 to 9). No patients in either group received rescue antiemetics during the study for a difference of 0% (95% CI, −5 to 5) (see Table 2).

4. Discussion

Morphine is an effective analgesic agent. However, its acceptance by patients and practitioners may be limited by side effects such as nausea, vomiting, and pruritus [3] Naloxone given in doses from 0.25 to 1.0 μg/kg per hour has been shown to attenuate these side effects when administered via the epidural or intrathecal routes and as IV PCA. Low-dose naloxone may reduce the total morphine required by postoperative patients and may have antinociceptive properties [5,7,21,22].

In addition, as summarized in Table 2, addition of low-dose naloxone (0.25 μg/kg) to therapeutic doses of morphine (0.1 mg/kg) was not associated with a statistically significant difference in our primary end point of nausea. Neither did we find statistically significant differences in our secondary end points of vomiting, pruritus, use of rescue antiemetics, or analgesia. Because the mean differences in measures of nausea, pruritus, and use of antiemetics were close to 0, the confidence intervals extended almost equally in negative and positive directions, consistent with no difference between the groups. The 1 skewed confidence interval was around the 4% difference in incidence of vomiting; however, it was the patients treated with naloxone who experienced more vomiting.

Table 2 Change in primary and secondary outcome variables between time 0 and 20 minutes

	Naloxone (N = 51), mean (95% CI)	Saline placebo (N = 48), mean (95% CI)	Difference between groups (naloxone-placebo), mean (95% CI)
Pain (mm) (95% CI)	−42 (−50 to −33)	−37 (−45 to −28)	−5 (−17 to 7)
Nausea (mm) (95% CI)	−13 (−20 to −6)	−14 (−21 to −6)	1 (−9 to 11)
Pruritus (mm) (95% CI)	1 (−1 to 3)	0 (−2 to 3)	1 (−3 to 3)
Vomiting (%) (95% CI)	4 (0 to 14)	0 (0 to 7)	4 (−1 to 9)
Use of rescue antiemetics (%) (95% CI)	0 (0 to 7)	0 (0 to 7)	0 (−5 to 5)

Since we began this study, new data have become available, indicating that the minimum clinically significant difference in our primary end point of nausea measured on a VAS is about 15 mm (95% CI, 11 to 20) [17]. This provides a clinical context within which to interpret our finding of a between-group difference in improvement of nausea of 1 mm (95% CI, −9 to 11) (see Table 2). Although the upper limit of this CI just reaches the lower limit of the CI for the minimum clinically significant difference in nausea reduction, the best estimate of the true difference in nausea is far more likely to be near the middle of the CI than toward its extremes [23], that is, around 1 mm. Such a small difference does not appear to be either clinically or statistically significant. In further support of this, a post hoc analysis of our sample size indicates that we had more than 99% power to detect a clinically significant difference in nausea, as defined by Donner et al [17], at the 2-tailed $\alpha = .01$ level, and still were unable to find such a difference.

With respect to differences in analgesia, as shown in Table 2, the difference in change in pain between the naloxone and placebo groups averaged −5 mm (95% CI, −17 to 7). Although the lower limit of this CI contains the threshold for the minimum clinically significant difference in pain reduction (about 13 mm) [19], the configuration and balance of the CI, combined with the location of the point estimate near the null, makes it extremely unlikely that 13 mm is the true difference between groups in change in pain [23]. Thus, it appears that the difference between the 2 groups in analgesia is neither clinically nor statistically significant.

Analgesic doses of morphine are thought to induce nausea. However, in our study, nausea decreased in both control and treatment arms despite achievement of clinically significant analgesia. We also found that the level of nausea as rated by the patients on visual analog scales was low both before and after administration of morphine. These findings are consistent with those of other recent studies, which found far lower levels of nausea with morphine administration in the ED than have been noted in other care settings [24-26]. Similarly, the incidence of vomiting associated with IV opioids was only 2% in our entire sample. This is in contrast to previously reported rates of 55%, reduced to 20% when low-dose naloxone was administered with morphine via a PCA pump [5].

We are unaware of any other ED study that has measured pain and nausea, 2 noxious sensations, simultaneously. Patients may not experience pain and nausea as 2 completely independent stimuli. By extension of this hypothesis, the reduction we noted in nausea, which was essentially the same with or without addition of low-dose naloxone, might be the result of increased overall comfort due to morphine-induced analgesia.

5. Limitations

Our study has several limitations. It is possible that we failed to find differences in opioid side effects, either because our naloxone dose or our choice of a 20-minute interval to measure outcome was not optimal. The selection of a 25-μg/kg bolus dose of naloxone was similar to doses given in previously effective regimens [5,8]. The 20-minute assessment interval was based on the half-life of naloxone and clinical consensus that morphine-induced nausea and vomiting was most likely to occur shortly after morphine administration [27]. It may be that the nausea typically attributed to morphine administration occurs either with prolonged exposure to morphine (as with repeated doses or a PCA morphine drip) or that the time at which IV morphine first induces nausea occurs beyond the 20-minute interval.

We did not gather information on the prophylactic administration of antiemetics given with the morphine in our study. Such administration is not standard practice in the EDs where the study occurred, and we do not believe such dosing took place.

We included in our study patients who had used opioids at home or within 6 hours of enrollment. Although it is not known whether prior, chronic, or recent exposure to opioids attenuates or augments the effect of low-dose naloxone, we do not believe that the presence of these patients in the data set is likely to have undercut the validity of our findings for 2 reasons: (1) as shown in Table 1, they appeared to be equally distributed between the 2 arms of the trial by randomization; and (2) when the data were analyzed without these patients the differences we found between the 2 groups as reported in Table 2 remained small and essentially unchanged.

6. Conclusion

Although all patients experienced marked reductions in acute pain, low-dose naloxone (0.25 μg/kg) administered

as an adjunct to IV bolus morphine (0.10 mg/kg) in the ED was not associated with a statistically or clinically significant reduction in nausea, vomiting, pruritus, or use of rescue antiemetics. These side effects may not be as common in the ED as they have been reported to be in other settings.

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