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REPORTS OF ORIGINAL INVESTIGATIONS

A naloxone admixture to prevent opioid-induced pruritus in children: a randomized controlled trial

Un mélange de naloxone pour prévenir le prurit induit par les opiacés chez les enfants: une étude randomisée contrôlée

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Abstract

Purpose *Morphine administered by continuous opioid infusion (COI) or by patient-controlled analgesia (PCA) is associated with opioid-induced pruritus (OIP). Intravenous naloxone administered separately to the morphine infusion at a dose of 0.25-1.65 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ can provide effective prevention from OIP. Nevertheless, this strategy requires a dedicated intravenous line and an additional infusion pump. The purpose of this study was to determine whether an admixture of naloxone with morphine in normal saline administered via COI or PCA would also prevent OIP in children without attenuation of analgesia or increased opioid utilization.*

Methods *In this randomized controlled trial, children meeting the inclusion criteria (aged 8-18 yr, American Society of Anesthesiologists physical status I-III, normal developmental profile and prescribed COI/PCA morphine for postoperative analgesia) were randomized to receive an infusion containing a naloxone, opioid, and saline admixture (NOSA) of 12 μg naloxone per 1 mg morphine per 1 mL normal saline or morphine only (control). The severity of opioid-induced pruritus was assessed by self-report using a modified colour analogue scale (mCAS; score 0-10). The groups were also compared for opioid utilization, pain scores, and administration of antipruritic medications, which were recorded for up to 48 hr or until the COI/PCA was discontinued.*

Results *Ninety-two participants were enrolled in the study. The median [interquartile range] dose of naloxone administered to the NOSA participants was 0.37 [0.30-0.48] $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The incidence of OIP, determined by self-report and treatment, was not different between groups: 22% in the NOSA group vs 36% in the control group (mean difference, −15%; 95% confidence interval [CI], −33 to 4; P = 0.164). The severity of opioid-induced pruritus was similar in the two groups, with a median difference in the participants' mean mCAS score of −0.29 (95% CI, −0.75 to 0.26; P = 0.509). Opioid utilization did not differ between groups, with a median difference of −1.35 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (95% CI, −5.85 to 7.55; P = 0.518), and pain scores did not differ, with a median difference of 0.0 (95% CI, −1.0 to 1.5; P = 0.659).*

Conclusion *This admixture of naloxone and morphine in normal saline did not decrease the incidence or severity of OIP in this sample. Separate administration of naloxone may be the more effective strategy for prevention of OIP. This trial was registered at ClinicalTrials.gov (NCT01071057).*

Author contributions *Nicholas West* performed the literature review, recruitment, and data collection. *Nicholas West* and *Guohai Zhou* contributed to the data analysis and drafted the article. *J. Mark Ansermino* and *Roxane R. Carr* designed the study. *Karen Leung* performed the randomization and supervised production of the study drug. *Gillian R. Lauder,* the primary investigator, contributed to the initial study concept and design and supervised the data collection. All authors reviewed the manuscript.

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Résumé

Objectif *La morphine administrée par perfusion continue d'opiacés (PCO) ou par analgésie contrôlée par le patient (ACP) est associée au prurit induit par les opiacés (PIO). On utilise de la naloxone intraveineuse en administration séparée de la perfusion de morphine à une dose de 0,25-1,65 μg·kg^{-1}·h^{-1} pour prévenir efficacement le PIO. Cependant, cette stratégie requiert une ligne intraveineuse dédiée et une pompe à perfusion supplémentaire. L'objectif de cette étude était de déterminer si un mélange de naloxone et de morphine dans un sérum physiologique administré par PCO ou ACP aurait les mêmes propriétés de prévention du PIO chez les enfants sans atténuer l'analgésie ou augmenter l'utilisation d'opiacés.*

Méthode *Dans cette étude randomisée contrôlée, les enfants répondant aux critères suivants: âgés de 8 à 18 ans, statut physique I-III selon l'American Society of Anesthesiologists, profil de développement normal, et auxquels on avait prescrit de la morphine en PCO/ACP pour l'analgésie postopératoire, ont été randomisés à recevoir une perfusion contenant un mélange de naloxone, d'opiacé et de sérum physiologique (NOSA) contenant 12 μg de naloxone par 1 mg de morphine par 1 mL de sérum physiologique ou de la morphine seulement (groupe témoin). La gravité du prurit induit par les opiacés a été évaluée par auto-questionnaire à l'aide d'une échelle analogique modifiée en couleur (EAmC; score 0-10). On a également comparé l'utilisation d'opiacés, les scores de douleur et l'administration de médicaments anti-pruritiques entre les groupes. Ces mesures ont été enregistrées jusqu'à 48 h ou jusqu'à interruption de la PCO/ACP.*

Résultats *Quatre-vingt douze participants ont été recrutés pour cette étude. La dose médiane [écart interquartile] de naloxone administrée au groupe NOSA était de 0,37 [0,30-0,48] μg·kg^{-1}·hr^{-1}. L'incidence de PIO, déterminée par auto-questionnaire et selon le traitement, était semblable dans les deux groupes: 22 % dans le groupe NOSA vs 36 % dans le groupe témoin (différence moyenne, −15 %; intervalle de confiance [IC] 95 %, −33 à 4; P = 0,164). La gravité du prurit induit par les opiacés était semblable dans les deux groupes, avec une différence médiane dans le score moyen des participants sur l'EAmC de −0,29 (IC 95 %, −0,75 à 0,26; P = 0,509). L'utilisation d'opiacés était semblable dans les deux groupes, avec une différence médiane de −1,35 μg·kg^{-1}·h^{-1} (IC 95 %, −5,85 à 7,55; P = 0,518) et les scores de douleur n'étaient pas différents, avec une différence médiane de 0,0 (IC 95 %, −1,0 à 1,5; P = 0,659).*

Conclusion *Ce mélange de naloxone et de morphine dans un sérum physiologique n'a pas réduit l'incidence ou la gravité du PIO dans cet échantillon. L'administration séparée de naloxone pourrait constituer une stratégie plus efficace pour prévenir le PIO. Cette étude est enregistrée au ClinicalTrials.gov (NCT01071057).*

Intravenous morphine administered either by continuous opioid infusion (COI) or by patient-controlled analgesia (PCA) is commonly used in multimodal therapy for the management of moderate to severe postoperative pain in children. Opioids such as morphine are associated with dose-related adverse effects, including nausea, vomiting, urinary retention, sedation, respiratory depression, constipation, and pruritus.[1,2] These adverse effects limit the utility of opioids because some patients consider the adverse reactions more distressing than the pain itself.[3] The reported incidence of opioid-induced pruritus (OIP) varies from 14-77%.[2-4]

Conventional interventions commonly used to treat OIP are inadequate. Administration of the antihistamine diphenhydramine has low efficacy and additional sedative effects that increase the risk of respiratory depression.[5] Conversion to an alternative opioid, such as hydromorphone, which is supported by observational studies and clinical experience,[6,7] may also pose additional risks to patient safety, including potential errors in the equianalgesic dosing of opioids.[6,8] Changing from intravenous to oral morphine may reduce some side effects, but it also provides less effective and/or inconsistent pain relief.

Naloxone administered as a low-dose (0.25-1.65 μg·kg^{-1}·hr^{-1}) intravenous infusion has been shown to reduce OIP in children, with greater evidence for its effectiveness as a preventative strategy than in the treatment of existing pruritus.[4] In the studies that have shown this strategy to be effective in children and adolescents,[3,9,10] the naloxone was administered at a fixed dose and as a separate infusion from the morphine. The widespread use of naloxone infusions to minimize OIP may have been hampered by the inconvenience of a separate infusion pump and tubing. Co-administration of naloxone and morphine as an admixture avoids this problem and provides naloxone dosing that matches opioid utilization. Compatibility of naloxone mixed with morphine has previously been established.[11]

Studies of naloxone-opioid PCA admixtures in adult patients have reported varying results, including poorer quality of analgesia,[12] no benefit,[13] or improved side effects with unchanged pain and opioid requirements.[14,15] Clearly, reducing adverse effects without compromising the quality of analgesia or increasing opioid consumption requires careful selection of the relative doses of naloxone and morphine. A dose-finding study in children showed that naloxone 1 μg·kg^{-1}·hr^{-1} was the minimum dose at which participants were successfully treated for OIP with

a < 10% failure rate and that 1.65 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ was as effective without increasing opioid requirements.[10] On the other hand, naloxone 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ has been found to increase morphine requirements in adults relative to 0.25 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ naloxone.[16]

The primary aim of this study was to determine whether a naloxone, opioid, and saline admixture (NOSA) containing 12 μg naloxone per 1 mg morphine in normal saline and administered via COI or PCA at a range of infusion rates would be effective in the prevention of OIP in children compared with morphine only (control). The secondary aim was to determine if NOSA administration would result in the attenuation of analgesia or increase opioid utilization.

Methods

Study population

Approval was obtained from the University of British Columbia Children's and Women's Research Ethics Board (May 2010) to conduct a double-blind randomized controlled trial. The participant cohort comprised children aged 8-18 yr and American Society of Anesthesiologists physical status I-III who were prescribed COI or PCA morphine for postoperative analgesia following surgery at British Columbia's Children's Hospital (BCCH). Children were excluded from the study if they had a known abnormal developmental profile, opioid allergy, pre-existing pruritus from a cause unrelated to opioid medication, or were involved in any investigational drug trial within the previous one month. Children on existing opioid therapy or requiring postoperative admission to the pediatric intensive care unit were also excluded. Informed parental consent and child assent were obtained for all participants, either at a pre-admission visit or in the hospital ward or surgical daycare unit before surgery.

Naloxone, opioid, and saline admixture study drug

At BCCH, the standard concentration of morphine in COI and PCA administration for patients over 30 kg is 1 $mg \cdot mL^{-1}$. Our Acute Pain Service (APS) policies dictate that morphine can be administered in the range of 0-150 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. A relative dose of naloxone to morphine was selected to ensure that the maximum dose of morphine administered could not result in a naloxone dose > 1.65 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, i.e., the maximum dose previously determined not to increase opioid requirements.[10] Hence, the NOSA concentration was set at 12 μg naloxone per 1 mg morphine per 1 mL normal saline. The physical and chemical compatibility of naloxone and morphine was confirmed in a preliminary study using high-performance liquid chromatography to show that the NOSA drug is stable for 72 hr at room temperature and 30 days with refrigeration.[11]

Participants were randomized to receive an infusion containing either morphine 1 $mg \cdot mL^{-1}$ in normal saline *with* naloxone 12 $\mu g \cdot mL^{-1}$ (NOSA group) or morphine 1 $mg \cdot mL^{-1}$ in normal saline *without* naloxone (control group). Participants were sequentially assigned to either the NOSA or the control group according to a computer-generated block randomization table that was accessible only to pharmacy personnel. The investigational products were labelled identically and had the same appearance. Participants, healthcare providers, and the study research assistant remained blinded to group allocation throughout the data collection phase of the study.

Anesthetic and pain management protocol

Preoperative medications, induction, and maintenance of anesthesia were administered at the discretion of the anesthesiologist. Intraoperative opioids included remifentanil, sufentanil, fentanyl, and morphine.

The study drug was prescribed for postoperative analgesia as a COI or PCA at the discretion of the anesthesiologist according to APS standard procedure. The COI dose range was 5-40 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ with intermittent rescue bolus doses of 10-20 $\mu g \cdot kg^{-1}$ every 30 min up to three consecutive doses. The PCA range was 10-20 $\mu g \cdot kg^{-1}$ for the PCA bolus dose and 3-20 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for a continuous background dose with a one hour limit up to 150 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Adjuvant medications were prescribed according to APS protocol: simple analgesics (acetaminophen, ketorolac, ibuprofen as appropriate); antiemetics (dimenhydrinate 0.5 $mg \cdot kg^{-1} \cdot dose^{-1}$ *iv q4h prn* and/or ondansetron 0.1 $mg \cdot kg^{-1} \cdot dose^{-1}$ *iv q8h prn*); and an antipruritic (diphenhydramine 0.5 $mg \cdot kg^{-1} \cdot dose^{-1}$ *iv q4h prn*).

The study drug infusion was commenced (at t_0) in the postanesthetic care unit (PACU) in accordance with standard opioid protocols. The study drug was not given intraoperatively or on first arrival in PACU as it would have been impossible to assess the potential effects of reduced analgesia and was against standard practice. Also, while in the PACU, rescue boluses of morphine (not study drug, regardless of group allocation) were administered before t_0 and up to one hour after t_0 if required to meet the individual pain management requirements of each child.

All participants' postoperative pain management was overseen by the APS throughout the study period. Adjustments to study drug doses were made according to the APS standard COI/PCA protocols, which allowed decreasing the PCA continuous background dose to 0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. If the COI/PCA infusion was discontinued or if any concurrent opioid medications

were administered, data collection was terminated and the participant was withdrawn from continued participation in the study.

Data collection

The incidence of pruritus was assessed every four hours in two ways: by self-report and by the need for the administration of antipruritic medication (i.e., diphenhydramine). The severity of pruritus was assessed by asking participants to rate their itchiness using a modified colour analogue scale (mCAS): the bottom end of the scale, interpreted as "no itch", was converted to a 0/10 score, while the top end, interpreted as "the most itch you can imagine", was converted to a 10/10 score. The mCAS has not been validated for pruritus assessment, but it has been used in a previous study[17] and is based on a standard self-report tool validated for pain assessment in children aged 5-18 yr.[18]

Opioid utilization was calculated from the infused volumes of COI/PCA. In addition, pain was assessed every four hours by self-report, numeric rating scale, colour analogue scale, or faces pain scale (revised) as appropriate and converted to a 0-10 metric. Heart rate, respiratory rate, blood oxygen saturation, arousal scores, and the administration of antiemetic agents (ondansetron and dimenhydrinate) were also recorded every four hours. Data collection was continued until the study was terminated up to a maximum of 48 hr (t_{48}).

Statistical analysis

At 0.8 power and alpha 0.05, the sample size required to detect a clinically significant reduction in the incidence of pruritus from 30% to 5% is 35 patients in each group. This large effect size was based on evidence from three key pediatric studies. Maxwell *et al.* showed a reduction in pruritus from 77% to 20% with the administration of only 0.25 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ naloxone.[3] The dose-finding study by Monitto *et al.* suggested that a higher dose of naloxone (optimally 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) would have a larger effect,[10] while Vrchoticky's retrospective review of 30 cases reported that 100% of children had received some benefit from the use of naloxone for the treatment of existing OIP, albeit with a relatively high mean (SD) dose [2.3 (0.7) $\mu g \cdot kg^{-1} \cdot hr^{-1}$].[9]

During the study, recruitment was continued in an effort to achieve $\geq$ 35 participants with $\geq$ 24 hr data per group.

A participant was judged to have experienced pruritus if itchiness was self-reported at any time during the study period (participant reported at least one mCAS score $\geq$ 1). Treatment for pruritus was judged to have occurred if a dose of diphenhydramine was administered at any time during the study. These two indicators of pruritus were also combined into a single indicator for pruritus, i.e., participant reported at least one mCAS score $\geq$ 1 and was treated with diphenhydramine, not necessarily concurrently. The occurrence of nausea was defined when at least one dose of an antiemetic agent was administered.

Binary outcomes are reported as *n* (%), and differences between groups were tested using the Fisher's exact test, including the primary outcome (incidence of pruritus) and secondary outcomes (treatment for pruritus, treatment for nausea). Numeric variables are presented as median [interquartile range; IQR], and as the data were not normally distributed, the difference between groups was tested using the Mann-Whitney U test, including the primary outcome (severity of pruritus) and secondary outcomes (pain scores, opioid utilization). The 95% confidence intervals (CI) for median differences were constructed using a percentile bootstrap[19] in which we repeatedly drew 10,000 bootstrap samples with replacement from the data, calculated the median difference for each bootstrap sample, and computed the 2.5th and 97.5th percentiles of these 10,000 median differences.

Survival analysis was used to analyze time to treatment with antipruritic medication. Logistic regression modelling was used to conduct *post hoc* analyses of observed imbalances in pruritus rates at baseline and pruritus rates among participants with different modes of administration (PCA or COI).

Statistical analysis was performed using SPSS® Statistics v17.0.0 (IBM, Armonk, NY, USA) and R v3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Ninety-two participants were enrolled in the study (Fig. 1) from March 2011-April 2013. Two participants were excluded: one required admission to the intensive care unit after randomization and another experienced an immediate skin reaction to the administration of a postoperative bolus of intravenous morphine and was switched to a hydromorphone infusion for ongoing pain management. Data collected from 46 participants randomized to the NOSA group and 44 participants randomized to the control group were analyzed (Table 1).

One participant (in the NOSA group) was switched to a hydromorphone infusion after 24 hr due to inadequate analgesia. For four participants, data collection was terminated due to concurrent opioid administration. One participant (control group) was given an intravenous bolus of morphine at t = 9 hr, and three participants were each given oral morphine, i.e., at t = 20 hr (control group), at t = 22 hr (NOSA group), and at t = 36 hr (NOSA group). In 50 participants, data collection was terminated when the COI/PCA infusion was discontinued before the end of the

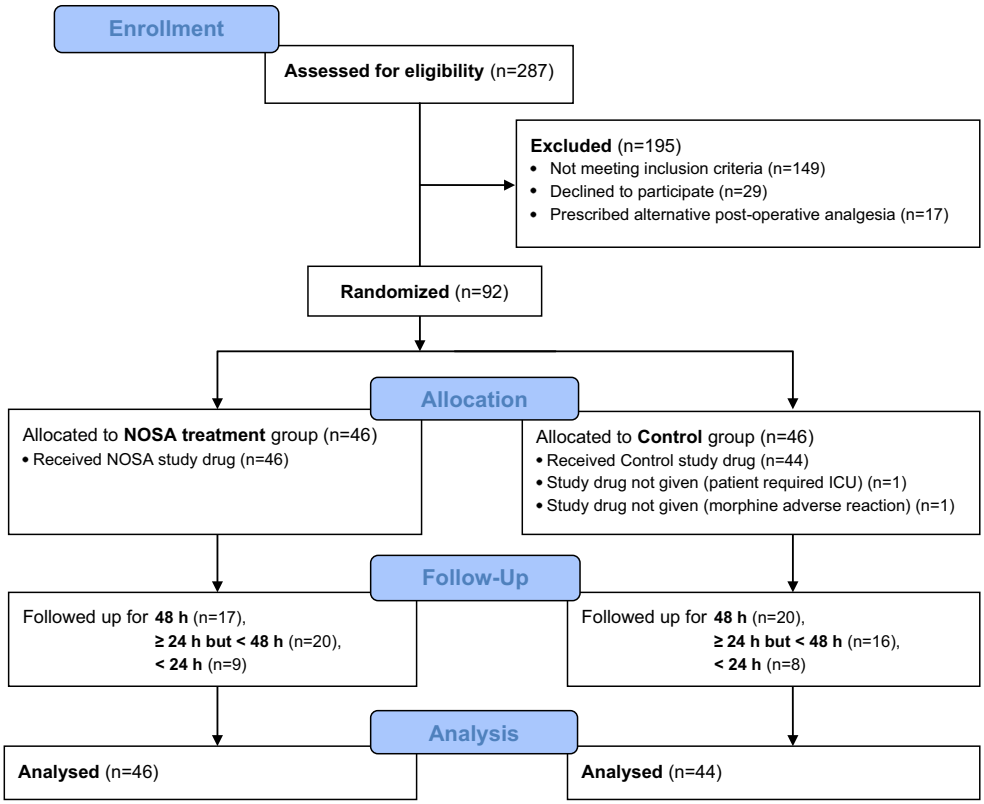

Fig. 1 CONSORT diagram describing enrolment, allocation, follow-up, and analysis of participants. NOSA = naloxone, opioid, and saline admixture

Table 1 Participant demographics, mode of analgesia, and surgical procedures

	NOSA group ($n = 46$)	Control group ($n = 44$)
Age (yr)*	14 [12-16]	15 [13-16]
Weight (kg)*	56.6 [44.4-64.0]	55.7 [44.0-67.3]
Sex (F / M)†	26 / 20	23 / 21
Mode (COI / PCA)†	15 / 31	12 / 32
Surgical procedure†		
General	4	9
Spine	15	12
Other orthopedic	23	19
Urology	3	4
Neurosurgery	1	0
Duration of study (hr)*	44 [24-48]	46 [24-48]

* Median [interquartile range; IQR]; †*n*

NOSA = naloxone, opioid, and saline admixture; COI = continuous opioid infusion; PCA = patient-controlled analgesia

study period. In the remaining 37 participants, data collection was terminated at t = 48 hr. Data were collected for ≥ 24 hr for 37 participants in the NOSA group and for 36 participants in the control group. Study duration was similar between the two groups (Table 1).

Incidence, severity, and treatment of pruritus

Incidence and severity of pruritus measured during the course of the study ($t_{4\text{-}48}$) were similar in the NOSA and control groups (Table 2). That is, there was no difference in the number of participants either self-reporting pruritus (mCAS ≥ 1) or treated for pruritus. The incidence of OIP, based on the combined indicator of both self-report and treatment, was 10/46 (22%) in the NOSA group and 16/44 (36%) in the control group (mean difference, −15%; 95% CI, −33 to 4; $P = 0.164$). Similarly, the severity of pruritus was not different between the two groups, with the median [IQR] of participants' mean mCAS scores being 0.44 [0.00-1.21] in the NOSA group and 0.74 [0.06-1.75] in the control group (median difference, −0.29; 95% CI, −0.75 to 0.26; $P = 0.509$) (Table 2).

Survival analysis showed no significant difference in time to treatment of OIP with diphenhydramine (log rank Chi square = 2.11; $P = 0.146$) (Fig. 2).

Pain, opioid utilization, and nausea

Participants' self-reported pain scores and opioid utilization did not differ significantly between groups (Table 3). Although the overall number of participants

Table 2 Incidence and severity of pruritus by group

	NOSA group ($n = 46$)	Control group ($n = 44$)	Difference (95% CI)	P value
Incidence of pruritus at baseline t_0[†]	10/46 (22%)	3/44 (7%)		
Incidence of pruritus $t_4 - t_{48}$[†]				
self-reported by participant (scored mCAS $\geq$ 1)	28/46 (61%)	33/44 (75%)	−14% (−33 to 5)	0.180
treated with diphenhydramine	12/46 (26%)	19/44 (43%)	−17% (−36 to 2)	0.121
combined indicator (both self-reported and treated)	10/46 (22%)	16/44 (36%)	−15% (−33 to 4)	0.164
Severity of pruritus $t_4 - t_{48}$*				
participants' mean mCAS score	0.44 [0.00-1.21]	0.74 [0.06-1.75]	−0.29 (−0.75 to 0.26)	0.509
participants' maximum mCAS score	2.00 [0.00-3.88]	2.25 [0.75-4.00]	−0.25 (−2.00 to 1.00)	0.425
area under the curve (AUC) mCAS score[‡]	15.50 [0.00-34.25]	19.00 [3.00-54.50]	−3.50 (−19.50 to 9.50)	0.517

* Median [interquartile range; IQR]; comparison based on median difference with confidence intervals from percentile bootstrap using 10,000 replications; P values from Mann-Whitney U test

† n (%); comparison based on mean difference, confidence intervals from Pearson Chi square test without Yates' correction and P values from Fisher's exact test (two-sided)

‡ The sum of each mCAS score multiplied by the duration across all time points for each participant

NOSA = naloxone, opioid, and saline admixture; CI = confidence interval; mCAS = modified colour analogue scale

treated for nausea was not significantly different between groups, a significantly greater number of control participants were treated with dimenhydrinate (Table 3).

Post hoc analyses

Differences in baseline pruritus and the impact of administration mode (COI or PCA) were analyzed *post hoc*.

The number of participants reporting itch (mCAS score $\geq$ 1) at baseline t_0 was substantially greater in the NOSA group than in the control group (Table 2). In order to adjust for this imbalance, at each time-point t_4 to t_{48}, we conducted a logistic regression with the incidence of OIP (defined as mCAS $\geq$ 1) as the dependent variable and included the baseline incidence of pruritus and group as independent variables. With this model, the NOSA group showed significantly reduced odds of OIP at t_{28} (odds ratio, 0.30; 95% CI, 0.10 to 0.92; $P = 0.035$), but not at any other time point (Fig. 3).

A further *post hoc* analysis suggested that the mode of administration (COI or PCA) made a significant contribution to OIP rates. The overall incidence of pruritus was only 1/27 (4%) among participants with a COI, but the incidence was 25/63 (40%) among participants with a PCA (mean difference, −36%; 95% CI, −50 to −22; $P < 0.001$) (Table 4). Nevertheless, a test for interaction revealed no significant difference for this effect between the two groups. That is, in a logistic regression model with the incidence of OIP as a dependent variable and with group, mode, and the group/mode interaction as independent variables, the interaction term was not found to be significant ($P = 0.993$).

Discussion

In this study, the effectiveness of a naloxone, opioid, and saline admixture (NOSA) was investigated using 12 μg naloxone per 1 mg morphine per 1 mL normal saline in preventing OIP in children aged 8-18 yr during the administration of morphine via COI or PCA for postoperative analgesia. Considering the number of participants requiring treatment for OIP and the time to first treatment for OIP, the incidence and severity of OIP were not significantly different between groups.

The overall incidence of pruritus was consistent with previous studies: 61/90 (68%) participants reported experiencing some degree of itch (mCAS score $\geq$ 1), and 31/90 (34%) participants received treatment for pruritus (Table 2). The incidence of OIP increased over the first 20-28 hr after starting the postoperative COI/PCA infusion. Similarly, 55/90 (61%) participants were treated for nausea during the study (Table 3). Managing these side effects of morphine presents challenges for patients, families, nurses, and doctors.

Participants in the NOSA treatment group received an admixture containing a low dose of naloxone that was matched to their opioid utilization. This approach, which is lacking in previous reports in a pediatric population, was considered an important factor to overcome wide variability in postoperative opioid consumption. For example, in our study, opioid utilization varied from a mean of 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ up to 82 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ across the duration of the study (Table 3). The admixture approach was also designed to overcome barriers to the adoption of low-dose naloxone as a routine preventative strategy by

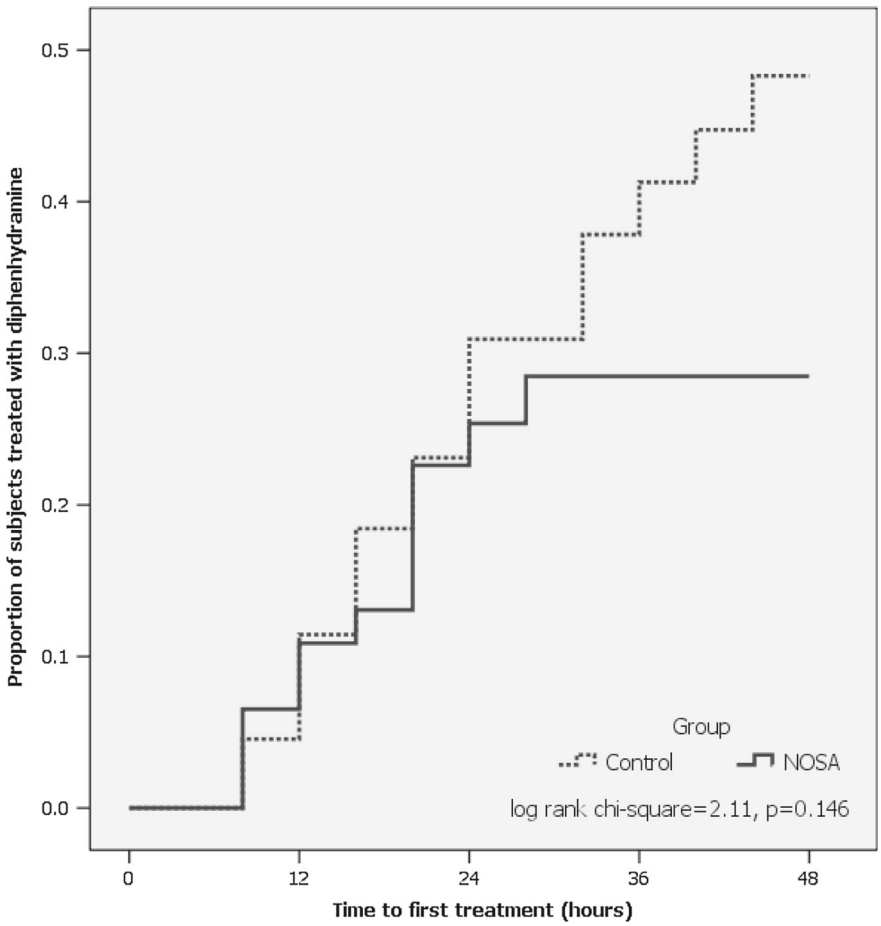

Fig. 2 Survival analysis showing time to first treatment for pruritus with diphenhydramine and treatment for opioid-induced pruritus (OIP) with diphenhydramine in each four-hour period $t_0 - t_{48}$. NOSA = naloxone, opioid and saline admixture

Number at risk	t_0	t_4	t_8	t_{12}	t_{16}	t_{20}	t_{24}	t_{28}	t_{32}	t_{36}	t_{40}	t_{44}	t_{48}
Control	44	44	42	38	35	33	23	20	18	17	16	14	11
NOSA	46	46	43	41	39	30	25	22	21	21	18	18	13

providing a convenient solution without the need for separate physicians' orders or additional intravenous administration requirements.

Nevertheless, a number of limitations may have affected the outcome of this study. First, the dose of naloxone in the admixture may have been too low (Table 3). That is, all participants in the NOSA group received a mean dose of naloxone that is less than the optimal dose of 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ identified in a previous dose-finding study.[10] Nevertheless, 42/46 (91%) participants did receive a dose greater than the 0.25 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ found to be effective in another study.[3] In both these previous studies, the naloxone was administered at a fixed dose. In the present study, the dose of naloxone was designed to adjust and correlate with the variable utilization of morphine. The relative dose of naloxone to morphine that we selected may have been conservative. Increasing the naloxone dose to reduce OIP must be balanced against the possibility of increasing pain or opioid consumption. A naloxone infusion of 1.65 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ is the maximum dose known to reduce OIP in children without increasing opioid requirements.[10] We calculated the dose of naloxone in the admixture based on the fact that we did not want to exceed 1.65 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ at the maximum dose of morphine (150 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) allowed by our current PCA settings. In practice, the maximum opioid dose is rarely achieved, although 11/90 (12%) participants in this study consumed > 100 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of morphine over at least one four-hour period. The dose of naloxone at which children's assessed pain or opioid requirements begin to increase is not clear, but one study found that 40% of participants reported increased pain and 17% of participants required an increase in their opioid dose when receiving a mean (SD) naloxone infusion of 2.3 (0.7) $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for treatment of existing OIP.[9] Limiting the maximum dose of opioid allowed might enable an increase

Table 3 Opioid utilization, pain, and nausea by group

	NOSA group ($n = 46$)	Control group ($n = 44$)	Difference (95% CI)	P value
Intraoperative opioid utilization* prior to t_0 ($\mu g \cdot kg^{-1}$)	112.0 [50.0-175.8]	104 .0 [45.0-161.5]		
PACU opioid utilization* prior to $t_0 + 1$ hr ($\mu g \cdot kg^{-1}$)	0.0 [0.0-54.0]	0.0 [0.0-44.5]		
Postoperative opioid utilization* during study $t_0 - t_{48}$ ($\mu g \cdot kg^{-1} \cdot hr^{-1}$)	31.1 [25.4-39.9]	32.5 [22.5-38.3]	−1.4 (−5.9 to 7.6)	0.518
Naloxone dose received* during study $t_0 - t_{48}$ ($\mu g \cdot kg^{-1} \cdot hr^{-1}$)	0.37 [0.30-0.48]			
Pain scores (self-report 0-10)* median pain score $t_0 - t_{48}$	2.5 [1.0-4.0]	2.5 [1.9-4.1]	0.0 (−1.0 to 1.5)	0.659
Treated for nausea $t_4 - t_{48}$†				
with ondansetron	25/46 (54%)	28/44 (64%)	−9% (−30 to 11)	0.399
with dimenhydrinate	10/46 (22%)	21/44 (47%)	−26% (−45 to −7)	0.014
treated with either drug	25/46 (54%)	30/44 (68%)	−14% (−34 to 6)	0.200

* Median [interquartile range; IQR]; comparison based on median difference, with confidence intervals from percentile bootstrap using 10,000 replications; P values from Mann-Whitney U test

† n (%); comparison based on mean difference, confidence intervals from Pearson Chi square test without Yates' correction and P values from Fisher's exact test (two-sided)

NOSA = naloxone, opioid, and saline admixture; CI = confidence interval; PACU = postanesthetic care unit

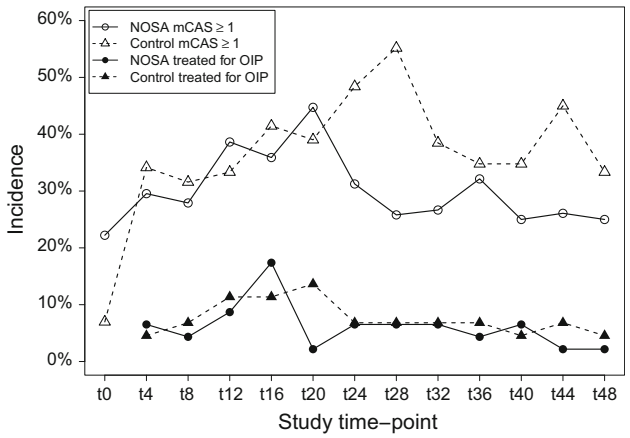

Fig. 3 Incidence of pruritus by group during the study period showing incidence by self-report (participant scoring itch with modified colour analogue scale [mCAS] ≥ 1) and by treatment for opioid-induced pruritus (OIP) with diphenhydramine in each four-hour period $t_0 - t_{48}$. NOSA = naloxone, opioid and saline admixture

in the relative dose of naloxone to morphine in an admixture.

Second, some factors not controlled in the study design may have had an impact on participants' OIP, including the administration of morphine prior to t_0 for intraoperative and postoperative analgesia. The randomized study admixture was not used intraoperatively or for immediate postoperative boluses, and morphine administration was not controlled during these periods. Morphine was given intraoperatively to 74/90 (82%) participants, and morphine boluses were administered postoperatively to 40/90 (44%) participants prior to (and up to one hour after) starting the study admixture in the PACU at t_0. The incidence of pruritus at study baseline t_0 was higher in the NOSA group (Table 2). Our analysis suggests that this imbalance may have affected the incidence of OIP during $t_4 - t_{48}$, but it did not sufficiently alter the balance of OIP between groups to change our conclusion, except at the time point (t_{28}) when the difference in reported pruritus was greatest (Fig. 3).

Third, another confounding factor that may have influenced the study results was the administration of dimenhydrinate. Dimenhydrinate contains diphenhydramine and, consequently, has antipruritic properties. Significantly fewer NOSA participants were given dimenhydrinate during the study period (Table 3). Although it was prescribed as an antiemetic, it will have had an effect on participants' OIP and potentially skewed the outcome data in this study.

Lastly, the determination of a clinically relevant reduction in OIP from 30% to 5% and the associated power calculation was perhaps optimistic and should be revised before any further trials are undertaken. It may be that a 50% reduction in the incidence of OIP would still be deemed clinically significant; however, showing such a reduction (from the 36% measured in our control group to 18%) would require a total sample size of approximately 190 participants (at 0.8 power, alpha 0.05). Recruiting such a sample in our institution would strain feasibility, especially as our data suggest that it is the population receiving PCA morphine (rather than COI) that should be the focus of future investigation. A larger multicentre trial may be warranted, possibly with a revised dose mix and taking into account the limitations of this study noted above.

There are complex interactions between pain and itch.[20] Opioid-induced pruritus may be mediated by a combination of effects, including histamine release, stimulation of opioid receptors in the central nervous system, and stimulation of

Table 4 Incidence of pruritus by group and mode of analgesia: continuous opioid infusion (COI) *vs* patient-controlled analgesia (PCA)

	COI	PCA	Difference (95% CI)	*P* value
NOSA group	0/15 (0%)	10/31 (32%)	−32% (−49 to −16)	0.019
Control group	1/12 (8%)	15/32 (47%)	−39% (−62 to −15)	0.032
All participants	1/27 (4%)	25/63 (40%)	−36% (−50 to −22)	< 0.001

All data presented as *n* (%); comparison based on mean difference, confidence intervals (CI) from Pearson Chi square test without Yates' correction and *P* values from Fisher's exact test (two-sided). NOSA = naloxone, opioid, and saline admixture

peripheral opioid receptors in the skin and/or the substantia gelatinosa of the spinal cord. Interaction at the level of the central nervous system is supported by the fact that mu-receptor antagonists such as naloxone have proven to be effective in the prevention of OIP.[4] Nevertheless, with such complex interactions, it may be too simplistic to assume that naloxone alone will be the sole remedy.

Interestingly, participants with a PCA experienced a much higher rate of OIP (25/63, 40%) compared with participants with a COI (1/27, 4%). This warrants further investigation using different PCA parameter settings to reduce side effects by minimizing large swings in opioid utilization without affecting the quality of analgesia.

In conclusion, the admixture of 12 μg naloxone per 1 mg morphine used in PCA and COI modes did not significantly reduce OIP compared with a control solution. This may be related to an inadequate dose of naloxone in the admixture, with a consequent smaller effect that this study was inadequately powered to detect. Consideration should be given to optimizing the dose mix of morphine and naloxone and conducting larger multicentre trials. Nevertheless, the unpredictable range of morphine doses required in the postoperative period may preclude the discovery of an acceptable admixture solution. Hence, we have recommended that a continuous infusion of naloxone 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, as suggested by previous research,[10] be started prior to the administration of any long-acting opioid to provide a more efficacious solution for OIP prevention.

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Conflicts of interest None declared.

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