The use of nalmefene for intrathecal opioid–associated nausea in postpartum patients

Intrathecal opioids (ITOs) are a safe and effective method of providing pain control to laboring parturients. The benefits of ITO include a rapid onset with a long duration of action during the first stage of labor, minimal effect on the progress of labor, and absence of motor blockade, permitting earlier ambulation and discharge from the hospital. The management of ITOs is less labor intensive than for epidural analgesia. Administration of ITOs is often the preferred technique at small to midsize community hospitals where anesthesia resources are limited.

Potential side effects of ITOs include pruritus, nausea, vomiting, urinary retention, and respiratory depression. Potential side effects of ITOs include pruritus, nausea, vomiting, urinary retention, and respiratory depression.

Pruritus, nausea, and vomiting are dose dependent and are the result of the presence of opioids in the cerebrospinal fluid or the vascular system. The presence of an opioid in the cerebrospinal fluid results in cephalad migration of the drug and subsequent interaction with the trigeminal nucleus in the medulla and opiate receptors in the area postrema, also known as the chemoreceptor trigger zone. Activation of the chemoreceptor trigger zone triggers the vomiting reflex by mechanisms that are not completely understood.

Chaney, in a 1995 review of the literature, reported a 30% incidence of nausea within 4 hours of injection of an ITO. This study suggested the incidence of nausea may be related to the dose of ITO used and may be higher when intrathecal morphine is administered, due to its hydrophilic properties and prolonged presence in the cerebrospinal fluid. In a similar study, Herpolsheimer and Schretenthaler examined the use of intrathecal fentanyl (25 µg) and morphine (250 µg) analgesia in laboring parturients. They concluded that ITOs provided satisfactory pain relief without disrupting the normal course of labor; however, the incidence of nausea was 44%.

A review of 99 parturients with spontaneous vaginal delivery who received intrathecal fentanyl (25 µg) and morphine (250 µg) for labor analgesia at our institution showed a 41% incidence of nausea and a 21% incidence of vomiting. The benefits of ITOs generally outweigh the side effects; however, finding viable treatments to reduce nausea and vomiting is of obvious importance.

A potential treatment for ITO-related side effects is the administration of an opioid receptor antagonist. Wittels et al compared the effects of opioid agonist-antagonists and pure antagonist administered immediately after umbilical cord clamping on maternal analgesia, overall satisfaction, and side effects after cesarean section with epidural morphine. An incidental finding of this study suggested that parturients who received naloxone, a long acting form of naloxone, had significantly less pruritus, nausea, and vomiting. Methylnaltrexone, a long-acting intravenous opioid antagonist that is structurally similar to naloxone, has been shown to significantly reduce the incidence of pruritus, nausea, and vomiting in postcesarean and postsurgical patients after administration of epidural or intravenous morphine, respectively.

Nalmefene, a methylated form of naltrexone, is an intravenous preparation with a terminal elimination half-life of approximately 10.8 hours. Frye et al examined the pharmacokinetics of nalmefene and found that it effectively reversed postoperative opioid respiratory depression without diminishing the analgesic response to subsequently administered opioids.
We therefore hypothesized that the administration of a long-acting opioid antagonist following labor analgesia with intrathecal opioids would reduce postdelivery nausea and vomiting. The specific aim of this study was to measure the severity of nausea using visual analog scale (VAS) scores and the incidence of emesis in subjects receiving intravenous nalmefene following labor analgesia with intrathecal fentanyl and morphine.

**Methods**

Following institutional review board approval, 60 ASA class I or II multiparous women older than 18 years of age were enrolled in this randomized, prospective, double-blind, placebo controlled study. Subjects were in active labor with cervical dilatation of 3 to 7 cm and uterine contractions increasing in duration and frequency, and they were requesting intrathecal labor analgesia. Parturients with a history of complicated pregnancy or chronic nausea or vomiting or who received opioid agonist or agonist-antagonist medication before administration of an ITO were excluded from the study. Data for subjects who requested or required additional analgesia after an ITO or required cesarean section were removed from the data pool.

Written informed consent was obtained from each subject. Consecutively numbered syringes that randomly contained either 20 mg of nalmefene hydrochloride (Revex, Ohmeda, Decatur, Ill) or an equivalent volume of normal saline were prepared by the pharmacy department. All subjects received 25 µg of fentanyl and 250 mg of preservative-free morphine intrathecally on request for labor analgesia. Data collection included age, weight, time of last meal, duration of labor (defined as time of admission to delivery), time of ITO administration, and total volume of intravenous fluids infused. A baseline VAS nausea score was obtained after subjects were enrolled.

Within 30 minutes after vaginal delivery, a VAS score was obtained and subjects received either 20 mg of intravenous nalmefene (experimental group) or an equivalent volume of intravenous normal saline (placebo group). Subjects were instructed in the use of the VAS tool, and a VAS score was obtained for the most severe episode of nausea that occurred before transfer to the postpartum ward, immediately before each meal, and at bedtime. Data were collected for the first 24 hours after delivery. Selection of the specific time intervals for VAS assessments provided similar postdelivery time periods for data analysis between groups. In the event of emesis, the time and whether treatment was requested were documented. Investigators observed each subject throughout the study to confirm adherence to the protocol.

The VAS tool for nausea consists of a 100-mm horizontal line anchored at one end with “no nausea” and with “worst nausea ever experienced” at the other end. Subjects were instructed to place a single vertical mark on the line indicating the severity of nausea experienced at the various time intervals.

Data were analyzed using descriptive and inferential statistics. Demographics and labor experiences were compared between groups using unpaired t tests. The VAS nausea scores were compared using an analysis of variance with the Bonferroni multiple comparison post hoc test. The incidences of emesis and treat-

### Table 1. Demographics*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 23)</th>
<th>Nalmefene (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Range</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>Age (y)</td>
<td>27 ± 5</td>
<td>20-39</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 ± 14</td>
<td>58-109</td>
</tr>
</tbody>
</table>

* No significant differences between groups (P > .05).

### Table 2. Study independent variables*

<table>
<thead>
<tr>
<th>Time intervals (min)</th>
<th>Placebo (n = 23)</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Nalmefene (n = 25)</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last meal to vaginal delivery</td>
<td>648 ± 326</td>
<td>164-1,203</td>
<td>778 ± 256</td>
<td>206-1,266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrathecal opioid to study drug injection</td>
<td>225 ± 146</td>
<td>65-555</td>
<td>189 ± 85</td>
<td>49-406</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of labor</td>
<td>342 ± 199</td>
<td>102-888</td>
<td>407 ± 245</td>
<td>54-899</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery to study drug injection</td>
<td>19 ± 8</td>
<td>3-33</td>
<td>17 ± 7</td>
<td>3-30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total intravenous fluids (mL)</td>
<td>2,184 ± 563</td>
<td>800-3,029</td>
<td>2,172 ± 633</td>
<td>800-3,800</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No significant differences between groups (P > .05).
Results
A total of 60 subjects were enrolled. Twelve subjects did not complete the study due to protocol violations. The majority of protocol violations resulted from subjects requiring additional analgesia after ITO administration or subsequent cesarean section.

Table 1 illustrates the demographic characteristics of the experimental and placebo groups. There were no statistically significant differences in demographic variables between groups (P > .05). Table 2 provides a comparison of independent variables between the 2 groups. The time from last meal to delivery, time from ITO administration to study drug injection, duration of labor, time from delivery to study drug administration, and total volume of intravenous fluids administered were compared. There were no statistically significant differences between the 2 groups (P > .05).

Figure 1 compares the mean VAS nausea scores between the experimental and placebo groups at various time intervals. These intervals included baseline obtained at enrollment, within 30 minutes after delivery, before transfer to the postpartum unit, before each meal, and at bedtime for the first 24 hours after delivery. There were no statistically significant differences in reported nausea severity between the groups at any time interval examined (P > .05).

Discussion
This study measured the severity of nausea and the incidence of emesis in subjects receiving intravenous nalmefene following labor analgesia with an ITO. The administration of nalmefene immediately after delivery did not reduce the severity of nausea or the incidence of emesis associated with ITO administration. This finding is in agreement with a study by Pellegrini et al,9 who concluded that 0.25 µg/kg of nalmefene did not reduce the incidence of ITO-related side effects following cesarean section and had a detrimental effect on postoperative analgesia.

There was a rising trend in mean VAS scores for the experimental and the placebo groups before transfer from the labor and delivery unit to the postpartum unit, which remained elevated at the time of the first postpartum reporting period. This may be attributed to the peak onset of intrathecal morphine. The rostral...
TREATMENT (n = 48; p = 0.05).

* There was no significant difference between groups in the incidence of nausea and/or emesis in the nalmefene (n = 25; treated, n = 11 [44%]) and the placebo (n = 23; treated, 6 [23%]) groups.

spread of morphine by passive flow with its subsequent effects on the chemoreceptor trigger zone often is cited as a cause of nausea after ITO administration. The time to reach peak brain concentration of morphine after ITO administration is approximately 3 hours. The mean time from administration of an ITO to transfer to the postpartum unit for all subjects was 258 ± 123 minutes. This places the transfer time and the postintrathecal morphine peak brain concentration within reasonable proximity and may account for the notable increase in both groups in VAS nausea scores at this time. The maximum plasma concentration of intravenous nalmefene is achieved approximately 5 to 15 minutes after administration with an elimination half-life of 10.8 hours. Although the peak plasma level of nalmefene would not have coincided with the peak concentration of morphine, there should have been a therapeutic level of nalmefene available at the time the VAS score was measured.

Although not statistically significant, subjects who received nalmefene generally had higher postpartum VAS nausea scores and were treated more frequently for nausea or emesis. One possible explanation is that nausea and emesis are potential side effects associated with nalmefene administration. The incidence of nausea in clinical trials was 18%. The intravenous administration of 20 µg of nalmefene immediately after vaginal delivery did not significantly alter the severity of nausea or the incidence of emesis following labor analgesia with intrathecal morphine and fentanyl. Based on these findings, we do not recommend the use of nalmefene in this manner. Areas for further research should include the delineation of a nalmefene dose-response curve, prophylactic administration before ITO administration, administration of a second rescue dose upon subject request, and nalmefene administration at a time that coincides with peak morphine levels in the brain.

REFERENCES


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