Transdermal Scopolamine Decreases Nausea and Vomiting following Cesarean Section in Patients Receiving Epidural Morphine

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The authors evaluated the antiemetic properties of transdermal scopolamine (TDS) in healthy patients undergoing elective cesarean section and receiving epidural morphine for postoperative analgesia. Prior to administration of anesthesia, 203 patients had either TDS or a placebo study patch applied behind one ear. All patients were hydrated with lactated Ringer’s solution iv and given 2.0% lidocaine with 1:200,000 epinephrine epidurally for surgical anesthesia. Following delivery of the infant, 4 mg of morphine sulphate was injected through the epidural catheter. After the operation patients were evaluated by “blinded” observers at 2, 4, 6, 8, 10, 24, and 48 h for nausea, vomiting, retching, pain relief, itching, and adverse effects. In addition, medications received were noted. No differences were found between the groups in terms of severity or incidence of pain, or requests for analgesic or antipruritic medication. Although there was no difference between the groups in the first 2 h, patients with TDS had significantly less nausea, vomiting, and retching than patients in the placebo group in each time interval between 2 and 10 h. Additionally, the TDS group required less antiemetic medication. There was no difference in the frequency of retching or vomiting between groups. Side effects were minimal and equal in both groups.

The authors conclude that TDS results in a decreased incidence of nausea and vomiting in patients who have delivered by cesarean section and received epidural morphine. TDS appears safe for continuous antiemetic administration. (Key words: Analgesics, epidural: morphine. Anesthesia: cesarean section; obstetric. Anesthetic technique: epidural. Parasympathetic nervous system: scopolamine. Vomiting, nausea: postoperative.)

Epidural morphine for postcesarean section analgesia is widely used.1–3 Despite excellent pain relief, the side effect of postoperative nausea and vomiting following epidural morphine is often distressing. The reported incidence of postoperative nausea and vomiting related to epidural opioids varies from 5% to 56%.2–5 Transdermal scopolamine (TDS) is widely used and is highly effective for controlling motion-induced nausea and vomiting. In a review of controlled studies of patients experiencing motion sickness,6–8 the therapeutic efficacy and pharmacodynamic properties of TDS were well demonstrated.

Based on these reports, this study was designed to assess the effectiveness of TDS in preventing nausea and vomiting associated with epidural morphine analgesia in patients undergoing elective cesarean delivery.

Materials and Methods

After institutional approval by the Human Subjects Committee and informed consent, 203 ASA physical status 1 or 2 patients, 18–38 yr of age and scheduled for elective cesarean section, agreed to participate in this randomized, double-blinded, placebo-controlled study. These nonmedicated patients had an iv catheter inserted, and 30 ml of sodium citrate po given in the preoperative area. An attending anesthesiologist applied the study patch behind one ear after wiping the skin clean with an alcohol swab. Patches were identical in appearance and size.

In the operating room patients were monitored with ECG, automatic blood pressure cuff (Omega®) at 1-min intervals, for 10 min, then every 5 min until completion of surgery, and continuous pulse oximetry (Nellcor®). After they received 1,500–2,000 ml of lactated Ringer’s solution iv, 2.0% lidocaine with 1:200,000 epinephrine was administered into the epidural space through a catheter inserted via L2–3 or L3–4 interspace. Patients were tilted to the left to displace the uterus, and surgical anesthesia to a dermatome level of T2–4 was documented. Systolic blood pressure was maintained at >100 mmHg by iv fluid administration or by intermittent iv doses of either ephedrine (5 mg) or mephentermine (7.5 mg).

After the neonate was delivered and uterine hemorrhage was achieved, 4.0 mg of morphine sulphate in 8 ml (Duramorph®) was injected through the epidural catheter. After the surgery blood loss was estimated and intraoperative nausea and vomiting were recorded. For efficacy evaluation, the point at which the patient arrived in the postanesthetic recovery room (PAR) was considered time zero. On average, this was 90 min following initial application of the study patch.

Efficacy was assessed at regular intervals after surgery by recording the times and durations of nausea, times and frequency of retching and vomiting, and the times of administration, doses, and routes of supplementary antiemetics. The first efficacy evaluation was made 2 h postoperatively in the PAR.

Subsequent evaluations were made 4, 6, 8, 10, and 24 h after surgery. An additional evaluation was made 24 h...
after removal of the patch to document all adverse experiences reported by the patient or recorded in the chart between 24 and 48 h postdelivery. During the final evaluation, the patients were asked if they had a history of motion sickness, nausea during pregnancy, or a tendency to nausea. A hematocrit was measured 24 h following surgery. Newborns were observed and received routine care in the nursery during the first 48 h after delivery.

Prophylactic antiemetics were not used. Supplemental droperidol im was only administered if the patient requested it. Vomiting and/or retching were the primary end point for efficacy analysis. Patients who received antiemetic medication continued to wear their patches for the full 24-h evaluation period. Intravenous administration of naloxone was permitted to control morphine-induced itching. Additional analgesics and other medications were allowed as indicated. The analgesic activity of morphine was monitored by soliciting the patient's assessment of severity of her pain at each time period, using the following rating scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain. Severity of itching was also assessed by the patient, using the following rating scale: 0 = none, 1 = mild, localized, 2 = moderate, 3 = severe, generalized.

At each efficacy evaluation period, the patient's chart was reviewed to determine if analgesic, antiemetic or other medications were given. The two groups, TDS and placebo, were compared and analyzed using the Mantel-Hanzel, two-sided t tests, two-sided chi-square tests, and two-sided Wilcoxon rank tests. P values of 0.05 or less were considered statistically significant.

Results

Differences between TDS and placebo groups with regard to age, week of gestation, weight, gravidity, neonatal weight, and Apgar scores were not significant. Among the potentially confounding factors for efficacy analysis in this study, the most important were intraoperative administration of additional opioids, postoperative administration of additional opioids, and postoperative administration of naloxone. There was no intergroup imbalance with regard to these variables.

Postoperatively, significantly fewer patients receiving TDS experienced nausea or retching/vomiting compared with those with a placebo patch in the four 2-h observation periods between 2–10 h with the exception of the 6–8 h period (figs. 1 and 2). Overall, during the first 24-h period, significantly fewer patients in the TDS group experienced nausea, vomiting, or retching (fig. 3) or requested additional antiemetic (fig. 4).

Patients in both groups similarly experienced no pain or mild pain postoperatively and requested additional analgesic. Mild to moderate pruritus was experienced by both groups, and requests for naloxone treatment were the same (table 1). Patients in both groups equally reported minor adverse experiences with the test patches (table 2). The occurrence of dry mouth was common, but patients were not specifically requested to indicate its severity. There was no correlation in the presence of nausea or retching/vomiting and intraoperative hypotension; intraoperative nausea or vomiting; surgical blood loss; preoperative and postoperative hematocrits; a history of
mation sickness; a history of general nausea; or a history of nausea during pregnancy.

**Discussion**

In our cumulative clinical experience prior to this study, we observed that women after cesarean delivery often complained of nausea and vertigo interspersed with sporadic vomiting. Despite having either no or mild pain with epidural morphine, it was clear that a more effective antiemetic would allow mothers to spend time comfortably with their newborns. This study reexamines TDS for postoperative nausea and vomiting. Loper et al. reported that in patients receiving epidural morphine following major gynecologic surgery, TDS patches significantly reduced the incidence and severity of nausea. The results of other studies have been equivocal.

Most of the patients who experienced nausea and vomiting did so by 10 h postoperatively. Inspection of the rates of symptoms/events (nausea, retching, vomiting, administration of antiemetics) in successive time intervals postoperatively reveals that with the exception of the 0–2 h interval, the differences in incidence rates are in favor of TDS at every postoperative evaluation interval up to 10 h postsurgery. All but one of these differences are statistically significant. We did expect to achieve significance in favor of TDS after the 2-h observation. On average, patches were applied approximately 210 min prior to this evaluation. Generally, it takes 3–4 h to achieve therapeutic blood levels of scopolamine.

Our highest incidence of nausea (44%) and vomiting (34%) was at the 2- to 4-h evaluation period in the placebo group, higher than reported in earlier series. Perhaps our incidence was higher because we observed and recorded any symptom episode as an occurrence. In non-obstetric postoperative patients receiving morphine epidurally, the incidence of reported nausea and vomiting is similar to ours. Stenseth et al. reported their experience with 1,085 patients who received morphine epidurally for postoperative pain. Their overall incidence of nausea or vomiting was 34% (range 12–56%), had no relationship with morphine dose, and varied with the type of surgery. Interestingly, postoperative nausea or vomiting was more frequent in women than in men (51% vs. 23%; P < 0.001). Bromage et al. reported that 60% of volunteers expe-

<table>
<thead>
<tr>
<th>Condition</th>
<th>TDS (n = 102)</th>
<th>Placebo (n = 101)</th>
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</thead>
<tbody>
<tr>
<td>No pain or mild pain</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>Request for analgesics</td>
<td>54</td>
<td>44</td>
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<tr>
<td>Report of pruritus</td>
<td>76</td>
<td>69</td>
</tr>
<tr>
<td>Request for naloxone for pruritus</td>
<td>40</td>
<td>43</td>
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*There were no significant differences.*
rienced nausea and 50% vomited 4–6 h after administration of 10 mg morphine epidurally.

The TDS patch is 2.5 cm² in area and 18 mm in diameter. It contains 1.5 mg of scopolamine and is designed to deliver in vivo 0.5 mg of scopolamine over 3 days. An initial priming dose (140 µg) of scopolamine released from the adhesive layer of the system saturates the skin binding sites and rapidly brings the plasma concentration of scopolamine to the required steady state level over 3–4 h. A continuous controlled release of scopolamine (5 µg/h), which flows from the drug reservoir through the rate-controlling membrane, keeps the plasma level constant. The anticholinergic effects of scopolamine may help prevent nausea by inhibiting vestibular input to the CNS and, in turn, the vomiting reflex. In addition, scopolamine may have a direct action on the reticular activating formation of the brain stem.

TDS has been applied for other medical indications that frequently result in severe nausea and vomiting. Results are available from two random blinded studies of TDS for cisplatin-induced emesis in cancer patients. Longo et al. reported acceptable side effects but ineffectiveness when used alone. Meyer et al. reported that the addition of TDS to a standard antiemetic regimen provides additive benefit in the control of cisplatin-induced emesis.

Common side effects reported when using TDS include dry mouth (67%), drowsiness (18%), and, less frequently, blurred vision. Although not seen in our study patients, a number of rare adverse effects of TDS have been reported. Toxic psychosis has been noted, particularly in elderly patients, and limited unilateral cycloplegia lasting up to 72 h has been described. One of our patients receiving TDS experienced mild, short-lived disorientation. She required no treatment and had the patch removed. Infants of mothers of both groups showed no adverse effects of the maternally applied transdermal patches.

In conclusion, TDS provides the patient a simple, painless, and continuously administered dose of scopolamine antiemetic. The patch significantly reduced but did not completely eliminate the occurrence of nausea and vomiting or retching. We recommend its use in the post-cesarean patient and believe that further evaluation is warranted in other postoperative settings.

References
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