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The morphine-sparing effect of metoclopramide on postoperative laparoscopic tubal ligation patients

Metoclopramide traditionally has been used as a prokinetic and antiemetic, but recently it also has been investigated as an agent to enhance analgesic efficacy. No definitive studies have been undertaken to determine whether metoclopramide can decrease postoperative analgesic requirements. The present study examined the effects of the administration of metoclopramide on the postoperative opioid analgesic requirements and pain intensity scores of patients following laparoscopic bilateral tubal ligation under general anesthesia.

Fifty-six subjects were enrolled in this double-blind, placebo-controlled, prospective study. Subjects were randomized into 2 groups, a control placebo group (n = 30) and an experimental metoclopramide group (n = 26), and were assessed for pain intensity using a numeric rating scale. Asessments were recorded at 3 time intervals. Total postoperative opioid requirements also were recorded.

Numeric rating scale pain scores were noted to be similar in both groups at all 3 time intervals examined. However, total postanesthesia care unit (PACU) morphine requirements were significantly higher in the placebo group than the metoclopramide group (P = .031). This study demonstrated that metoclopramide administered preoperatively can significantly decrease morphine requirements in the PACU but had no impact on pain intensity as rated by numeric rating scale pain scores.

Key words: Analgesia, metoclopramide, pain measurement, postoperative pain, tubal sterilization.

Advances in anesthesia and operative techniques have made ambulatory surgery routine. Surgical procedures that, in the past, were associated with long-term hospitalization are now performed as same-day procedures with patients being discharged to home a few hours following surgery. Foremost among these same-day surgical procedures is laparoscopy. According to Bradford et al,[1] one third of all gynecological operations are now performed by laparoscope. Postoperative problems after laparoscopic tubal ligation commonly include significant pain, nausea, and vomiting.[1,2] These problems are routinely treated with the administration of parenteral opioids and antiemetic agents, which themselves can cause adverse effects and increase hospital time.

Metoclopramide is perhaps best known for its ability to increase gastric motility. By blocking central and peripheral (intra-abdominal) dopamine receptors and increasing acetylcholine release or muscarinic receptor sensitivity, metoclopramide causes increased peristalsis and reduces smooth muscle spasm.[3,4] The antiemetic properties of metoclopramide also have been well studied and are attributed to its action on dopamine (D_2) receptor blockade in the chemoreceptor trigger zone, on its weak 5-HT_3 antagonism, and its ability to empty the stomach.[4] However, when compared with other antiemetics, its efficacy in this role is minimal.[5]

Interestingly, studies have shown that metoclopramide exhibits analgesic activity in animals exposed to both chemical and thermal injury. These studies attempted to analyze the specific mechanism by which metoclopramide produces analgesia.[6] It has been shown that antag-

onism of the dopaminergic system by metoclopramide results in prolactin release in animals and humans, which is believed to contribute significantly to the analgesic action of the endogenous opioid system. The ability of naloxone, a mu receptor antagonist, to reduce metoclopramide-mediated analgesia in animals corroborates opioid system involvement.[6]

Metoclopramide's analgesic properties in humans are less well known, and the mechanism by which metoclopramide modulates the pain response is unclear. Metoclopramide is thought to increase acetylcholine levels at neuroeffector junctions and postganglionic nerve terminals by inhibiting the action of acetylcholinesterase. The mechanism and the extent to which metoclopramide encourages acetylcholine release is unknown.[7] Acetylcholine may be involved in the body's modulation of pain control, affecting central mu, kappa, and delta receptors. Current opioid research focuses on determining exactly how opioids function at receptor sites and how acetylcholine and dopamine are involved in this process.[8] The complexity of this question makes it difficult to isolate the relationship of metoclopramide in opioid function, pain modulation, and analgesia. However, patient satisfaction might be improved if postoperative pain and nausea could be diminished, and this could potentially result in earlier discharge from the ambulatory care setting.[1]

A number of studies have evaluated the prokinetic and antiemetic properties of metoclopramide. However, evidence that metoclopramide has analgesic or analgesic-enhancing properties is limited. At least 1 study suggested a direct role for metoclopramide as an analgesic,[6] and others allude to a possible indirect or

adjunctive effect.[1,3,9-11] No definitive studies have evaluated the analgesic effect of metoclopramide when given to patients undergoing laparoscopic procedures. The primary objective of the present study was to evaluate the ability of preoperatively administered metoclopramide to decrease analgesic requirements in the postanesthesia care unit (PACU). This was measured by a numeric rating scale (NRS) for pain intensity and analysis of morphine requirements in subjects undergoing laparoscopic bilateral tubal ligation.

Methods

After institutional review board approval, 56 adult women, ASA physical status I or II, gave their consent and then enrolled in this study. Included in the study were English-speaking women, aged 18 or older, who were scheduled through the ambulatory procedure unit for laparoscopic bilateral tubal ligation, and who requested general anesthesia. Individuals with a history of chronic pain, psychiatric disorder, or acute or chronic nonsteroidal anti-inflammatory or opioid drug use were excluded from the study. Patients with known allergies to any of the protocol drugs also were excluded. Subjects were randomized into 2 groups by the pharmacy department, using a computer-generated randomization program.[12] The pharmacy then prepared a 50-mL 0.9% sodium chloride solution alone or with 10 mg of metoclopramide. The researchers administered the number-coded solution prior to general anesthesia. All subjects, researchers, surgeons, and nursing staff members were blind to the content of the intravenous (IV) admixtures obtained from the pharmacy.

The NRS for pain intensity is a standardized psychometric instrument that utilizes an 11-point pain intensity scale (0-10) and allows subjects to verbalize the degree of their pain intensity. Zero depicts "no pain" and 10 indicates "pain as bad as it can possibly be."[13] This measure of pain intensity correlates highly to the well-accepted visual analog scale (VAS) and is considered reliable and valid as a measure of pain intensity for clinically acute pain. The NRS is simple to use, easy to score, and can be administered verbally.[13-15] Pain intensity was rated by each subject. An NRS pain score was verbally determined before anesthesia induction, on admission, and on discharge from the PACU. The baseline NRS pain score was obtained from each subject in the preoperative holding area before IV catheter placement. The appropriate IV admixture was administered over a 20-minute period before anesthesia induction. Midazolam, 2 mg IV, was given for preoperative anxiolysis.

A standard general anesthesia protocol was followed for all subjects. This included an intravenous induction with fentanyl, 2 μg/kg; lidocaine, 1 mg/kg; propofol, 2 mg/kg; and rocuronium, 0.4 to 0.6 mg/kg. Endotracheal intubation was performed after it was determined that adequate neuromuscular blockade was present, as evidenced by the patient's response to peripheral nerve stimulation. An oral gastric tube was placed to suction, and anesthesia was maintained with 50% oxygen, 50% nitrous oxide, and 0.5% to 1.0% isoflurane. Tubal ligations were performed using clips (Hulka-Clemens or Filshie) or fallopian tube rings by either the single- or dual-puncture laparoscopic technique. Two types of trocars were used, cutting or step type, and the same surgeon performed all but 6 of the tubal ligations. After induction, ketorolac, 30 mg IV, was given to all subjects. Subjects were extubated after meeting standard criteria. Subjects who required reversal of neuromuscular blockade received neostigmine, 0.05 mg/kg, with glycopyrrolate, 0.01 mg/kg IV.

Subjects who requested pain medication while in the PACU were treated with morphine, 1 to 3 mg IV, every 5 minutes to a total dose of 0.1 mg/kg. Subjects sensitive to morphine could receive meperidine IV, and the dose was converted to morphine equivalents for comparison between groups. Additionally, meperidine IV, 12.5 mg, was given to subjects who had uncontrolled rigors/shivering, for a total of 2 doses or 25 mg. For nausea or vomiting, all subjects had standardized orders for administration of ondansetron IV, in 2-mg increments every 15 minutes, up to 8 mg or to resolution of symptoms. Frequency data were collected on the number of subjects who received ondansetron.

Data were collected over a 4-month period, and demographics were collected on each subject. Multivariate analysis of variance was used to compare groups with regard to NRS pain scores; total morphine use; total PACU, anesthetic, and surgical times; and differences in operative technique. A chi-square test was used to analyze the incidence of nausea and vomiting between groups. The data are expressed as median or mean ± SD. An alpha of less than .05 was considered significant.

Results

Of the 56 subjects enrolled in this double-blind, placebo-controlled, prospective study, 26 were in the metoclopramide group, and 30 were in the placebo group. No differences were noted between groups in demographic variables, surgical operative time, anesthesia time, or total length of stay in the PACU (Table 1).

Between-group analysis showed that the median NRS pain score preoperatively was 0 (0) for the placebo group and 0 (0-2) for the metoclopramide

Table 1. Demographic data

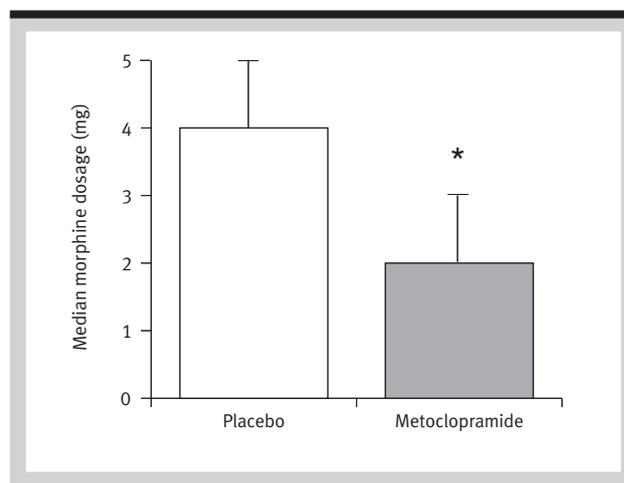|	Placebo group (n = 30)	Metoclopramide group (n = 26)
Age (y)	29 ± 5	30 ± 5
Height (in)	65 ± 3	65 ± 3
Weight (kg)	75 ± 15	70 ± 13
Surgical duration (min)	28 ± 13	26 ± 3
Total time in post-anesthesia care unit (min)	56 ± 27	55 ± 24

group (P=.539). The median NRS pain score on PACU admission was 3 (0-10) for the placebo group and 1 (0-8) for the metoclopramide group (P=.178). The median NRS pain score on PACU discharge was 3 (0-7) for the placebo group and 3 (0-7) for the metoclopramide group (P=.161). Analysis of NRS pain scores showed no significant differences in pain intensity between groups at any time period examined (Figure 1).

The mean total PACU morphine dosage consumed by the metoclopramide group (2.1 ± 0.53 mg) was significantly lower than the placebo group (4.0 ± 0.76 mg, P=.031) (Figure 2). Other variables that were analyzed included operative technique and infiltration of local anesthetic. A single trocar insertion site was used in 40 (71%) subjects, while 16 (29%) received a second trocar insertion site. Hulka-Clemens or Filshie clips were used in 41 (73%) subjects, while the remainder received fallopian tube rings. Skin incisions were infiltrated with 0.25% bupivacaine in 89% of subjects, and 20% of these subjects also received local anesthetic to the fallopian tubes. The omission of bupivacaine in 6 cases (11%) resulted in increased pain scores and analgesic requirements even when a single incision technique was compared with a dual incision technique (P=.046). The metoclopramide and placebo groups were equally represented among the 6 subjects who did not receive bupivacaine and also between the single- and dual-incision techniques. Operative technique, fallopian tube disruption, and infiltration of local anesthetic were not found to be influential factors on NRS pain scores or total morphine requirements between the 2 groups (P=.271).

Individual dosing regimens were analyzed between groups. Of a total of 30 subjects in the placebo group, 21 (70%) required 1 dose of morphine, 16 (53%) required a second dose, 12 (40%) required a third dose, and 7 (23%) required a fourth dose to attain

Figure 1. Comparison of median numeric rating scale (NRS) pain scores between the placebo and the metoclopramide groups upon arrival in the postanesthesia care unit (PACU) and upon discharge from the PACU*
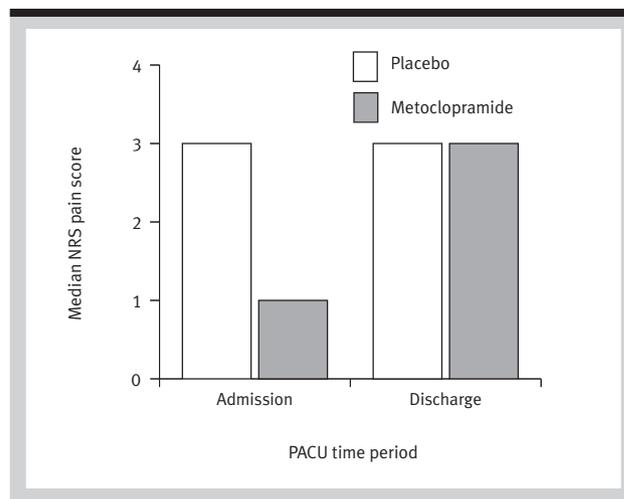
*There was no significant difference in median NRS pain scores between groups at either of these time periods (N = 56, P > .05).

Figure 2. Comparison of mean morphine dosage used between the placebo and the metoclopramide groups during the postanesthesia care unit stay

*The mean morphine dosage used by the metoclopramide group was significantly less than the mean morphine dosage used by the placebo group during this time period (N = 56, *P = .031).

adequate analgesia. For the placebo group, an average dose of 2.3 mg of morphine was given at each of the 4 time intervals.

In the metoclopramide group, which included 26 subjects, 12 (46%) required a first dose of morphine, 9 (35%) required a second dose, and 4 (15%) required a third dose of morphine. An average of 2.2 mg of morphine was given at each of these 3 time intervals in the metoclopramide group. No subject in the meto-

clopramide group required a fourth dose to attain adequate analgesia in the postoperative setting. The mean times to first request for analgesia were 32 minutes in the placebo group and 42 minutes in the metoclopramide group ($P=.245$) (Table 2). The only statistically significant difference noted between groups was the time to fourth dose of morphine ($P=.008$).

Nine subjects (30%) in the placebo group required ondansetron for nausea, while only 4 subjects (15%) required ondansetron in the metoclopramide group. Therefore, the percentage of subjects requiring treatment for nausea was significantly higher in the placebo group compared with the metoclopramide group ($P=.022$).

Morphine was the only opioid used for control of postoperative pain. All subjects received ketorolac, and no subject required meperidine for pain. No subjects in either group developed hypotension or respiratory depression. All subjects reported satisfactory analgesia in the PACU. No subjects were excluded from analysis for sensitivity to metoclopramide, history of Parkinson disease, or failure to follow study protocol.

Discussion

Based on our data, metoclopramide extended the duration of clinically effective analgesia and decreased overall morphine requirements in the PACU by 50% in this patient population. The data are consistent with previous animal[6,16,17] and human studies.[3,10] Rosenblatt et al[10] demonstrated a 66% decrease in analgesic requirements when metoclopramide was used at the time of prostaglandin-induced termination of pregnancy.

Other studies suggest that metoclopramide has no analgesic efficacy. Lisander[11] studied the analgesic effect of metoclopramide in subjects undergoing knee arthroscopy. The data showed a decreased analgesic requirement in the metoclopramide group. The author speculated that the primary anesthetic was responsible for the analgesic effect and was not influenced by the addition of metoclopramide. It is interesting to note that the theoretical mechanism of action for the analgesic effect of metoclopramide is through an increase in central acetylcholine release, yet Lisander[11] administered atropine, a cholinergic antagonist, before induction. Driver et al[18] and Danzer et al[19] both concluded that metoclopramide did not significantly reduce morphine requirements and had no impact on VAS pain scores following cesarean section. Since the half-life of metoclopramide is 4 to 5 hours, timing and amount given may be important. Blood levels of metoclopramide may not remain high enough to confer analgesic-sparing properties for the time intervals in which pain intensity was measured

Table 2. Morphine requirements between groups

	Placebo group (n=30)	Metoclopramide group (n=26)
First dose requirements (No. and %)	21 (70)	12 (46)
Minutes to first dose (mean)	32	42
Second dose requirements (No. and %)	16 (53)	9 (35)
Minutes to second dose (mean)	43	56
Third dose requirements (No. and %)	12 (40)	4 (15)
Minutes to third dose (mean)	73	94
Fourth dose requirements (No. and %)	7 (23)	0 (0)
Minutes to fourth dose (mean)	104	N/A*

Times are denoted in mean minutes from the time of administration of placebo or metoclopramide to subject request for supplemental analgesia in the postanesthesia care unit.
* Not applicable; no subject in the metoclopramide group required a fourth dose of morphine.

or analgesic use was documented in these studies. Danzer et al[19] also conceded that physiologic responses to dopamine and dopamine antagonists vary throughout pregnancy. Thus, results may differ in second-trimester or nonpregnant patient populations. Resolution of this conflict may require definitive laboratory studies that isolate an effect of metoclopramide on a specific opioid receptor and/or pain pathway.

Based on the findings in these studies and in the present study, metoclopramide is efficacious in affording analgesic-sparing effects for women undergoing laparoscopic gynecological procedures, but it may not be as efficacious for other types of surgeries. A comparative analysis performed by Bradford et al[1] analyzed the effect of metoclopramide, scopolamine, bupivacaine, and ketorolac on the overall level of analgesia. These investigators described a reduction in pain intensity, as measured by VAS pain scores. However, the lower VAS pain scores correlated better with the subject's level of nausea than with the subject's level of analgesia. In this present study, significantly fewer subjects in the metoclopramide group required treatment for nausea or vomiting than the placebo group. Decreased incidences of retching, nausea, or

vomiting, therefore, could be important factors that directly affect perceived pain intensity levels and morphine requirements.

The present study was conducted primarily among young, active duty military subjects or other women eligible for care at military treatment facilities. The US military population and family members comprise a diverse group, yet this sample does represent some limitation in the ability to extrapolate to the general population. However, no significant demographic differences existed between the subject groups studied. Another potentially confounding variable was that 40 tubal ligations were performed using a single-puncture laparoscopic technique. This may have had a direct influence on the degree of postoperative pain because, typically, a dual-puncture technique is used for laparoscopic tubal ligations. Only 16 procedures were performed using the dual-puncture laparoscopic technique. Of those 16 who underwent the dual puncture technique, 10 were in the placebo group, and 6 were in the metoclopramide group. In future studies, the technique of fallopian tube disruption also should be controlled, because a difference in pain intensity may exist between clips (Hulka-Clemens or Filshie) and fallopian tube rings or other surgical techniques. No significant differences were noted in either morphine requirements or NRS pain scores with regard to technique; however, these subgroups were small. Length of surgery was not a factor in determining postoperative morphine requirements or NRS pain scores. The mean duration of surgery was approximately 26 minutes in the metoclopramide group and approximately 28 minutes in the control group.

The primary purpose of the present study was to determine whether the administration of metoclopramide could decrease the morphine requirements in the PACU and decrease the total time a patient stays in the PACU. While the present study clearly demonstrated morphine-sparing properties, it failed to shorten the PACU stay significantly. Many factors may affect PACU stay time, such as shift change delays, availability of transport personnel, and protocols that dictate a minimum stay requirement. Better measures than documented transfer times from the PACU, such as Aldrete scores, could be used; however, small time changes may not be clinically significant.

Metoclopramide also was found to have antiemetic-sparing properties, although this action might be attributed to the reduction of opioids administered to the metoclopramide group. The dual effects exhibited in the present study could translate to a decrease in postoperative morphine requirements and a decrease in use of costly antiemetics. Although not examined in this present study, metoclopramide use could contribute to an anesthetic plan designed to shorten hospital stay, decrease patient costs, and increase patient satisfaction.

REFERENCES

1. Bradford TH, Robertson K, Norman PF, Meeks GR. Reduction of pain and nausea after laparoscopic sterilization with bupivacaine, metoclopramide, scopolamine, ketorolac, and gastric suctioning. *Obstet Gynecol.* 1995;85:687-691.

2. Malins AF, Field JM, Nesling PM, Cooper GM. Nausea and vomiting after gynaecological laparoscopy: comparison of premedication with oral ondansetron, metoclopramide and placebo. *Br J Anaesth.* 1994;72:231-233.

3. Rosenblatt WH, Cioffi AM, Sinatra R, Saberski LR, Silverman DG. Metoclopramide: an analgesic adjunct to patient-controlled analgesia. *Anesth Analg.* 1991;73:553-555.

4. Brunton LL. Agents affecting gastrointestinal water flux and motility; emesis and antiemetics; bile acids and pancreatic enzymes. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed.* New York, NY: McGraw-Hill; 1996:932-933.

5. Domino KB, Anderson EA, Polissar NL, Posner KL. Comparative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting: a meta-analysis. *Anesth Analg.* 1999;88:1370-1379.

6. Ramaswamy S, Bapna JS. Analgesic effect of metoclopramide and its mechanism. *Life Sci.* 1986;38:1289-1292.

7. Watanabe AM. Acetylcholine receptor stimulants. In: Katzung BG, ed. *Basic and Clinical Pharmacology.* 3rd ed. East Norwalk, Conn: Appleton & Lange; 1987:64.

8. Simon EJ. Opioid peptides and their receptors. In: Estafanous FG, ed. *Opioids in Anesthesia II.* Boston, Mass: Butterworth-Heinemann; 1991:23-24.

9. Mecklem DWJ. Propofol injection pain: Comparing the addition of lignocaine or metoclopramide. *Anaesth Intensive Care.* 1994;22:568-570.

10. Rosenblatt WH, Cioffi AM, Sinatra R, Silverman DG. Metoclopramide-enhanced analgesia for prostaglandin-induced termination of pregnancy. *Anesth Analg.* 1992;75:760-763.

11. Lisander B. Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia. *Br J Anaesth.* 1993;70:631-633.

12. Norusis MJ. *SPSS for Windows Based System User's Guide Release 6.0.* Chicago, Ill: SPSS Inc; 1993.

13. Paice JA, Cohen FL. Validity of a verbally administered numeric rating scale to measure cancer pain intensity. *Cancer Nurs.* 1997;20:88-93.

14. Flaherty SA. Pain measurement tools for clinical practice and research. *AANA J.* 1996;64:133-140.

15. Jensen MP, Karoly P, O'Riordan EF, Bland F Jr, Burns RS. The subjective experience of acute pain. An assessment of the utility of 10 indices. *Clin J Pain.* 1989;5:153-159.

16. Ghelardini C, Fantetti L, Malcangio M, Malmberg-Aiello P, Giotti A, Bartolini A. Involvement of central cholinergic neurotransmission in metoclopramide analgesia. *Pharmacol Res.* 1992;25(suppl 1):25-26.

17. Xu ZB, Pan YY, Xu SF, Mo WY, Cao XD, He LF. Synergism between metoclopramide and electroacupuncture analgesia. *Acupunct Electrother Res.* 1983;8:283-288.

18. Driver RP Jr, D'Angelo R, Eisenach JC. Bolus metoclopramide does not enhance morphine analgesia after cesarean section. *Anesth Analg.* 1996;82:1033-1035.

19. Danzer BI, Birnbach DJ, Stein DJ, Kuroda MM, Thys DM. Does metoclopramide supplement postoperative analgesia using patient-controlled analgesia with morphine in patients undergoing elective cesarean delivery? *Reg Anesth.* 1997;22:424-427.

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