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Morphine After Tubal Ligation With Bupivacaine: Dosage Versus Body Weight

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ABSTRACT

Background and Objectives: We investigated whether there was a statistically significant difference in patient need for postoperative analgesia based on adjusted body weight between heavier and lighter women who underwent laparoscopic tubal ligation with bupivacaine injection at the skin incision.

Methods: We examined 49 records of women who underwent laparoscopic tubal ligation at Oklahoma State University Medical Center between 2000 and 2005 and received an injection of bupivacaine at the surgical site during the procedure. Postsurgical morphine was measured as doses per kilogram of body weight against total body weight and as total milligrams per kilogram of body weight against total body weight. A regression was performed for each measurement.

Results: Heavier women required significantly fewer total milligrams of morphine per kilogram of body weight and fewer total doses of morphine per kilogram of body weight than lighter women (2-tailed $P = .0035$ and $P = .0018$, respectively).

Conclusion: Our data may suggest that lipophilic bupivacaine injected at a surgical site is held in place better and works for a longer period when more fat is present.

Key Words: Bupivacaine, Morphine, Postoperative analgesia, Tubal ligation.

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INTRODUCTION

In the United States, most tubal ligations are performed laparoscopically with patients under general anesthesia on an outpatient basis. Multiple factors have been implicated regarding postoperative pain after laparoscopic tubal ligation, including distension-induced phrenic neurapraxia, an acidic intraperitoneal environment during the operation, residual intra-abdominal gas, humidity, temperature and volume of the insufflated gas, wound size, drains, anesthetic drugs, postoperative effects, and sociocultural and individual factors.[1]

At Oklahoma State University (OSU) Medical Center, laparoscopic tubal ligations are performed with patients under general anesthesia. In addition, most of our physicians elect to give their patients a pre-emptive injection of bupivacaine as a local anesthetic at the wound site during the operation for pain control on awakening. Pain is further managed postoperatively with one of several opioids or opiates, such as morphine.

The purpose of this pilot study was to determine retrospectively whether there was a statistically significant difference in patient need for postoperative analgesia based on adjusted body weight between heavier and lighter women. We hypothesized that the anesthetic injection of lipophilic bupivacaine during surgery could affect heavier women differently than lighter women so that their postoperative analgesia needs, adjusted as milligrams or doses required per kilogram of body weight, would be proportionately lower. The null hypothesis was that the amount or number of doses would be proportional to patients' body weight.

MATERIALS AND METHODS

This study was approved by the OSU Center for Health Science Institutional Review Board. The requirement for written informed consent was waived by the Institutional Review Board. This study was a retrospective chart review of all eligible female patients, aged 21 to 52 years, who underwent laparoscopic tubal ligation by the Falope-ring (Olympus Gyrus, Center Valley, PA) method at a medical center in Tulsa, Oklahoma, between January 1, 2000, and December 31, 2005. The women had been patients at the

nearby affiliated clinic and typically lived in an urban area and were uninsured. Most were white, African American, or Native American. The data were available because they had been collected for another study with an unrelated purpose.

At OSU Medical Center, laparoscopic tubal ligation is performed with the patient under general anesthesia. Two trocars are typically used: A 5-mm trocar is placed umbilically, and a 7-mm trocar is placed suprapubically. Surgical procedures are usually performed by residents under the supervision of an attending physician. The eligible patients in our study had also received a pre-emptive local anesthetic injection of up to 15 mL of 0.5% bupivacaine for postsurgical analgesia along with epinephrine for vasoconstriction. This injection was administered subcutaneously, just after the surgical procedure and before the patient awakened. None of the patients in our study was given ketorolac at any time.

After tubal ligation, 1 of 4 possible narcotics is typically administered for pain control: meperidine, morphine, buprenorphine, or hydromorphone. For the sake of uniformity, we only included patients who received morphine as their postoperative analgesic. The total maximum number of postoperative morphine doses possible was 6, and the minimum was 0. Morphine was delivered by intravenous injection in 2- to 5-mg increments, depending on the nurses' expert assessment of patient need for pain relief. In summary, this study included women who underwent outpatient, laparoscopic tubal ligation at the medical center between 2000 and 2005; who received an injection of bupivacaine at the surgical site during the procedure for postsurgical analgesia; who received morphine for postsurgical analgesia; and who received no other pain medications. Excluded were women with the following comorbid conditions because they may alter patients' pain levels or their perception of pain after the tubal ligation: history of chronic pelvic pain, history of pelvic inflammatory disease, opiate abuse, conversion to an open procedure, unsuccessful tubal ligation, laceration of a tube, placement of >1 ring on a single tube, admittance to the hospital, additional procedures performed, endometriosis, and allergy to lidocaine or bupivacaine.

Postoperative morphine dosages given were quantified in 2 ways: (1) by conversion to total milligrams administered per kilogram of body weight and (2) by total doses administered per kilogram of body weight. Because height was not included in the data collected in the original but unrelated study, body mass index (BMI) could not be calculated. Regressions were performed to compare the 2 groups' mean adjusted milligrams of postoperative morphine administered and their mean adjusted doses administered.

The study from which these data were obtained was registered with ClinicalTrials.gov. The assigned identification number was NCT01062087.

Two regressions were performed: (1) total milligrams of morphine received after surgery per kilogram of body weight versus total body weight and (2) total number of doses of morphine received after surgery per kilogram of body weight versus total body weight. Statistics were calculated using SAS software, version 9.2 (SAS Institute, Cary, North Carolina). The significance level chosen was the standard $P < .05$.

RESULTS

Forty-nine patient records met the inclusion criteria for the period examined. The mean amount of bupivacaine injected was 5.04 mL (0.5% solution), and the SD was 3.79 mL. There was no correlation between this local amount of bupivacaine with epinephrine injected and the women's weight ($P = .53$). Variability was attributable to the preference and experience of the surgeon. The mean total morphine dose received was 6.74 mg (SD, 4.87 mg; 95% confidence interval [CI], 6.03 to 7.45 mg). The mean body weight was 81.43 kg (SD, 25.55 kg; 95% CI, 74.28 to 88.58 kg). The slope calculated for total milligrams of morphine per kilogram of body weight versus total body weight was −0.0012 ($t = -3.07$; 2-tailed $P = .0035$; $df = 47$; 95% CI, −0.0019 to −0.0004) (**Figure 1**). The coefficient of determination, r^2, was 0.17. In other words, 17% of the variability in the values for milligrams of morphine per kilogram of body weight could be explained by the variability in the women's body weights. The slope calculated for total doses of morphine per kilogram of body weight versus total body weight was -4.7×10^{-4} ($t = -3.32$; 2-tailed $P = .0018$; $df = 47$; 95% CI, -7.5×10^{-4} to -1.8×10^{-4}) (**Figure 2**). The coefficient of determination, r^2, was 0.19. In other words, 19% of the variability in the values for total doses of morphine per kilogram of body weight is explained by the variability in the women's body weights.

DISCUSSION

We found a statistically significant negative relationship between body weight and adjusted milligrams of morphine and between body weight and adjusted number of doses of morphine. In other words, heavier women re-

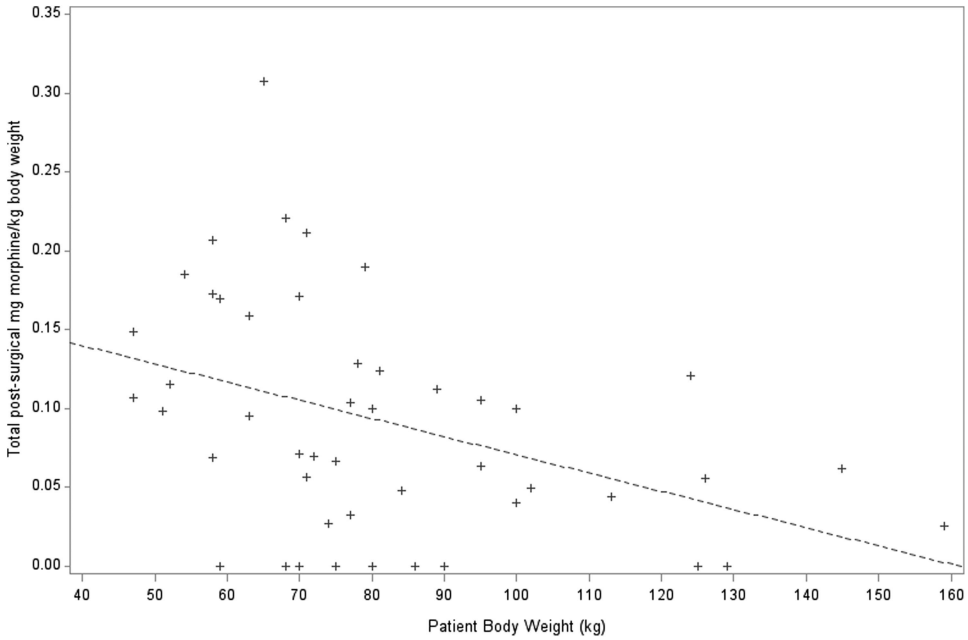

Figure 1. Regression of patient weight versus total postsurgical milligrams of morphine adjusted for body weight. All patients (N = 49) received injection of bupivacaine at the surgical site during surgery.

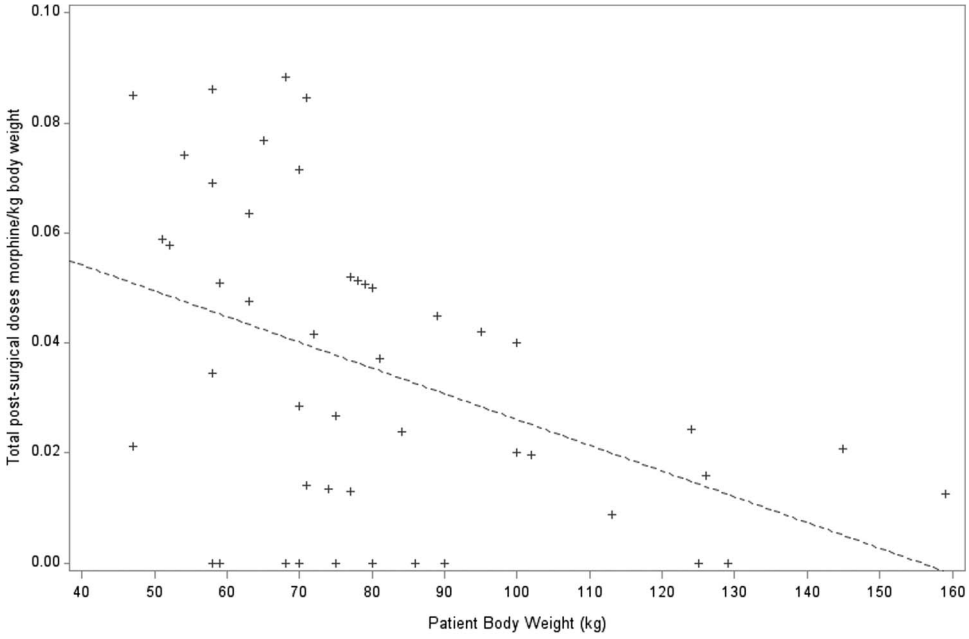

Figure 2. Regression of patient weight versus total postsurgical morphine doses adjusted for body weight. All patients (N = 49) received injection of bupivacaine at the surgical site during surgery.

quired far less morphine, proportionally speaking, when compared with lighter women, than what would be expected under a model of a constant value per kilogram of body weight. Likewise, heavier women required proportionally fewer doses of morphine, when compared with lighter women, than what would be expected using a model of a constant number of doses per kilogram of body weight. In short, our results showed that heavier

women required significantly less morphine for postoperative analgesia, measured either as total number of doses or as adjusted milligrams per kilogram of body weight, than their lighter counterparts. Without BMI data, it cannot be known with certainty whether the heavier patients had a higher quantity of abdominal adipose, on average, than the lighter patients. An alternative explanation could be that the heavier women, on average, were taller or had greater muscle mass than the lighter women. However, if we assume that the heavier women had more abdominal fat, on average, than the thinner women, it is possible to submit a physiologically sound explanation for our results. Perhaps the key to understanding our significant and counterintuitive findings could lie in the pharmacologic properties of the anesthetic injection agent, bupivacaine, rather than the postsurgical morphine itself.

Previous studies have been unable to agree on whether anesthetic injection during surgery reduces the need for postsurgical analgesia. Several prospective, controlled studies have examined pre-emptive (and also typically multimodal) analgesia for laparoscopic tubal ligation. Some of these have concluded that measures such as local anesthetic wound infiltration are superior for pain control to waiting to administer analgesics until the patient awakens and has pain.[2–15] No retrospective studies on this topic could be located. However, 2 meta-analyses involving many studies of pre-emptive analgesia for a variety of surgery types did not support the conclusion that adding a local anesthetic during surgery is superior to merely using postsurgical analgesia.[16,17] Furthermore, some studies specifically examining the use of bupivacaine or ropivacaine during laparoscopic tubal ligation did not find them superior to placebo in reducing postsurgical pain.[18–20] Finally, at least 2 studies concluded that local analgesia does, in fact, decrease postoperative pain but the timing of its administration, either presurgically or postsurgically, is not significant.[21,22] In short, although multimodal analgesia is generally accepted as more effective than any single analgesic alone,[23] pre-emptive analgesia per se is still controversial.[17]

Our data may bring clarity to this confusion for the following reasons: Bupivacaine is highly lipid soluble, being 95% bound to proteins when in plasma because of its hydrophobic nature.[24] In a comparison of the lipophilicity of 8 local "caine" anesthetics, including both esters and amides, bupivacaine was second only to etidocaine. Bupivacaine's lipid solubility coefficient was 28, as compared with 2.9 for lidocaine, which came in third, and a mere 0.02 for procaine, which came in eighth.[25] We postulate that when a bupivacaine injection is given to a woman with a relatively high deposition of abdominal fat near the surgical site, the drug is held in place by its affinity for the adipose tissue. Its lipophilic nature allows it to be passively absorbed by the adipose cells, to remain relatively unchanged in the metabolically inactive adipocytes, and then to passively leave the cell again with random Brownian movement, creating a short-term reservoir of bupivacaine. Furthermore, recent data indicate that the adipose tissue of some obese individuals contains fewer capillaries than the adipose tissue of leaner individuals.[26]

Supporting the aforementioned idea is the finding that the high lipid content of nervous tissue causes it to take up anesthetics that are relatively lipid soluble, such as bupivacaine, better and more quickly than less lipid-soluble anesthetics.[27,28] The increased uptake then dilutes the concentration gradient, decreases the likelihood of absorption into the plasma, and prolongs the duration of the drug.[25] In the same way, we postulate that women with more abdominal fat might expect to receive a greater effect of this local anesthetic for a longer period than their thinner counterparts, thus reducing the heavier women's need for postsurgical analgesia.

Another relevant characteristic of bupivacaine that may shed light on our results is that it is a relatively potent vasodilator.[8] Although this vasodilation would be counteracted somewhat by epinephrine in vascular tissue, it could still increase the likelihood of the venous removal of the bupivacaine itself from the site of its injection.[8] We postulate, therefore, that when bupivacaine is injected in a patient with a lower quantity of abdominal adipose, this drug is taken up by the vascular system more quickly and becomes unavailable for continued anesthesia earlier than in a patient with more, relatively less vascular adipose[26] to both solubilize it and prevent its access to the vascular system.

There are potential clinical applications to our findings. If it can be confirmed that overweight patients receiving bupivacaine later require less postoperative narcotic medication than those who do not receive bupivacaine, then surgeons might routinely choose to administer injections of bupivacaine in obese patients as the standard of care. The need for fewer opiates after surgery would be advantageous for obese patients, in particular, because they have a higher incidence of postoperative complications from these drugs than thinner patients.[29,30] For example, obese patients are at greater risk of gastric aspiration and pneumonitis, as well as hypoxia and hypoventilation.[29,30] Furthermore, obese patients have a higher risk of deep vein thrombosis (DVT) and the potential for pulmonary

embolism than thinner patients,[30] both of which underscore the need for early postoperative ambulation. Ambulation can be accomplished much sooner if the patient is not nauseated and vomiting, which are other common complication of opioids or opiates.[31] Finally, patients needing less narcotic medication after surgery could be ready for discharge from the hospital sooner than those requiring more narcotic medication.

An alternative possibility to explain these results is that the nursing staff charged with administering morphine in the recovery room was, either consciously or subconsciously, limiting the amount of morphine they gave to heavier patients as much as possible because of concerns about respiratory depression and DVT, as previously mentioned. It seems unlikely, however, that heavier patients would have been consistently undermedicated because they would have undoubtedly expressed their discomfort, asked for relief, or complained later of insufficient care. Even so, this potential bias could be partly overcome in a prospective study with specific criteria for drug administration and provides a strong reason why the topic should be investigated further, as well as why this article must serve as a stimulus for further research on this topic.

We acknowledge the following weaknesses of our study: Because the study was retrospective, certain factors were less uniform than the design of a prospective study might have been. For example, the operations were performed by several physicians, some of whom were residents. Their techniques and preferred dosages of bupivacaine varied, although as stated in the "Materials and Methods" section, there was no statistical relationship between the dose of bupivacaine and patient weight. Furthermore, the amount of postoperative analgesic administered was somewhat subjective because it was determined by nursing staff based on a visual assessment and by monitoring patient vital signs. In addition, it is possible that not all patients were truly opioid naive if they failed to report drug abuse, and therefore some could have had a tolerance to narcotics that caused them to require higher dosages than normal. However, given the small, significant *P* value obtained, we do not believe the study's weaknesses call into question our conclusions.

CONCLUSION

If we make the assumption that heavier body weight may correlate in general with a greater quantity of abdominal adipose tissue, our findings could indicate that bupivacaine injection at the surgical site before laparoscopic tubal ligation is more effective at reducing the need for postsurgical analgesia in heavier women than in thinner women. We postulate that the greater the amount of abdominal fat, the longer this anesthetic may be held in place and the longer it acts. If further studies using BMI can verify this hypothesis, surgeons might be better equipped to provide effective pre-emptive pain relief in the subset of patients with higher amounts of abdominal fat, perhaps sparing them complications from postsurgical narcotic use in the process.

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