Preoperative Intravenous Morphine Sulfate With Postoperative Osteopathic Manipulative Treatment Reduces Patient Analgesic Use After Total Abdominal Hysterectomy

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Context: Administration of opioids for treatment of pain after total abdominal hysterectomy (TAH) is a common postoperative procedure, providing an excellent parameter for evaluating the efficacy of postsurgical osteopathic manipulative treatment (OMT).

Objective: To determine whether a combination of preemptive morphine sulfate and postoperative OMT could provide improved analgesic effects.

Design: Randomized double-blind controlled trial.

Setting and Patients: Thirty-nine hospitalized patients assigned to one of four treatment groups: (1) preoperative saline and postoperative sham manipulative treatment; (2) preoperative saline and postoperative OMT; (3) preoperative morphine and postoperative sham manipulative treatment; or (4), preoperative morphine and postoperative OMT.

Intervention: Saline (control) or morphine, 10 mg, delivered intravenously (IV) 10 minutes before surgical incision. All patients received a postoperative patient-controlled IV analgesia pump containing morphine. At specified intervals following preoperative IV injections, blood was drawn and analyzed for morphine concentrations. Subjects were also asked to rate their postoperative levels of pain, nausea, and vomiting.

Results: There were no differences in either pain, or nausea and vomiting scores among the four study groups. Patients in Group 4 used less morphine than those in the Group 3 for the first 24 hours (P=.02) and from 25–48 hours (P=.01) after elective TAH. Morphine blood concentrations were lower after 24 hours in Group 4 compared with Group 2 (P=.04).

Conclusion: Administration of postoperative OMT enhanced pre- and postoperative morphine analgesia in the immediate 48-hour period following elective TAH, demonstrating that OMT can be a therapeutic adjunct in pain management following this procedure.

Optimal treatment of patients with postoperative pain remains a challenge to all healthcare professionals, but researchers have been investigating approaches to minimizing postsurgical pain and increasing analgesic effects. A 2003 study by Bardiau et al suggests that creation of a system for acute pain management can improve analgesia in this period. The purpose of the present study is to determine whether a combination of preemptive morphine sulfate and postoperative osteopathic manipulative treatment (OMT), an understudied procedure itself, can enhance postsurgical analgesia following elective total abdominal hysterectomy (TAH).

Preemptive analgesia has been shown to increase patient comfort after surgery. More than a decade ago, Wall proposed that pain during surgery appears to facilitate stimulation of dorsal horn neurons, or “central sensitization,” and may be a causative factor in postoperative pain. In this regard, it has been shown that administration of analgesics immediately before an operation can reduce postsurgical pain.

In 1988, McQuay et al reported that giving opioid medication or local anesthetics preoperatively in elective orthopedic surgery significantly increased the time for a patient’s first request for a postoperative analgesic compared with those patients receiving no such treatment. The time before first request was increased even further when a combination of opioid and local anesthetic was administered.

Bach et al demonstrated that patients who received a lumbar epidural block of bupivacaine and morphine before limb amputation were pain free for one year after surgery (ie, the follow-up period) compared with patients who did not receive this pretreatment.

In a study of patients who underwent nonemergent colectomy, Simpson et al reported patients who received epidural morphine before surgery used less morphine in the 48-hour postoperative period compared with patients who did not receive preoperative analgesic treatment. Furthermore, pretreated patients waited longer than the nonpretreated group in the postoperative period before requesting additional morphine.

Preoperative analgesia and postoperative pain patients who undergo TAH has been studied previously. In the 24-
hour period following elective TAH, Richmond et al\textsuperscript{6} documented use of less total postoperative morphine (ie, patient-controlled analgesia) in patients who received 10 mg morphine intravenously (IV) or intramuscularly (IM) before surgery compared with those given the same IV morphine dose postsurgically. Although both types of preoperative morphine treatment produced a reduction, statistical significance ($P < .05$) occurred only with preemptive IV morphine.\textsuperscript{6}

From a 1996 pilot study on 17 patients who underwent elective TAH, Goldstein et al\textsuperscript{7} demonstrated that the use of preemptive IV morphine, when compared with a preemptive IV control (saline), reduced administration of postoperative patient-controlled analgesia—consequently resulting in relatively lower blood concentrations of morphine, as measured by radioimmunoassay, in the immediate 48-hour postoperative period. In 1998, Karamanlioglu et al\textsuperscript{8} administered rofecoxib (a cyclooxygenase-2 [COX-2] selective inhibitor) or placebo orally to patients before they underwent abdominal hysterectomy. Both pain scores and use of postoperative tramadol hydrochloride were significantly lower in the rofecoxib group.\textsuperscript{8}

Although presurgical analgesia has been shown to reduce patient need for postsurgical analgesia, OMT might help further reduce postoperative pain. Achieving viscerosomatic and somatovisceral reflexing may be the most important consideration when determining the osteopathic manipulative (OM) techniques available for use in this context because patients may present with these reflexes stimulated for three obvious reasons. First, a patient could have a documented pathological history that led to the recommendation for surgery. That pathological history may have already produced a heightened response (ie, afferent input to the spinal cord and higher centers) that may also have caused neural and vascular changes in areas that are of common spinal innervation.

Second, muscle tension may be increased in these areas, and other tissue texture changes and pain may have also occurred, as identified by DiGiovanna et al,\textsuperscript{9} Kuchera,\textsuperscript{10} Hobbs et al,\textsuperscript{11} and Sato.\textsuperscript{12}

Third, the surgical operation itself can be causative of other events, such as inflammation, pain, and muscle guarding.\textsuperscript{13} The surgical procedure, therefore, has the potential of adding to a previously heightened response (ie, afferent

\textbf{Figure 1.} Patient body weight (kg) before surgery. Values presented are arithmetic averages with 95% confidence intervals.
approved this pilot prospective, double-blind, randomized, controlled clinical investigation and its consent form. All procedures employed were in accordance with established ethical standards for human experimentation (Declaration of Helsinki of 1975 and 1983 revision).15 Patients who elected TAH and who met all of the following eligibility requirements were recruited for this investigation as outlined below.

**Inclusion criteria:**
- aged 18 years or more,
- expected length of hospital stay at least 48 hours,
- able to self-report pain levels,
- able to request medications, and
- unfamiliar with OMT as a treatment modality.

**Exclusion criteria:**
- liver disease,
- kidney disease, or
- receiving antidepressant therapy (eg, clinical depression and/or chronic pain syndrome).

Thirty-nine patients volunteered for this double-blind study, met all eligibility requirements, and signed the consent form. Participants were assigned to one of the four study groups according to a predetermined randomized sequence:

**Materials and Methods**
Before the hospital’s closing on May 1, 2000, the City Avenue Hospital (Philadelphia, Pa) Institutional Review Board input to the spinal cord), causing more adverse events (eg, pain, spasm, and edema) than would be expected by the pathologic condition or the surgical intervention alone.

Using OMT postoperatively in these patients has the potential of diminishing the possibility of triggering the somatic component. Thus, there would be a decrease in stimulation of somatic afferents and an attenuated activation of nociceptors.9,14 Reducing or eliminating altered somatic and efferent reflexing and nociceptor stimulation should result in less somatic reactivity (eg, muscle spasm) and pain in patients. To test whether there is any benefit to simple touching of patients—or placing the hands on them—sham manipulative treatment was also performed in the present study.

To the best of our knowledge, this is the first time that a combination of preemptive morphine and postoperative OMT has been employed to enhance postsurgical analgesia following elective TAH.

**Figure 2.** First 24 hours after surgery (0–24 hours): total postoperative dose of morphine sulfate (mg/kg). Values presented are arithmetic averages with 95% confidence intervals.
Group 1 (Saline and Sham Treatment)
Group 2 (Saline and Osteopathic Manipulative Treatment)
Group 3 (Morphine Sulfate and Sham Treatment)
Group 4 (Morphine Sulfate and Osteopathic Manipulative Treatment)

* P value as reported is Group 4 compared to Group 3.

Figure 3. Second 24 hours after surgery (25–48 hours): total postoperative dose of morphine sulfate (mg/kg). Values presented are arithmetic averages with 95% confidence intervals.
Gentle myofascial release treatments were then performed to ensure free range of motion of the sacrum and equalize fascial tension in all directions until tissue relaxation and sacral motion were optimized. Likewise, this step was not administered for longer than 5 minutes on patients in Groups 2 and 4.

Sham manipulative treatment was performed on patients in Groups 1 and 3, also with patients in the supine position. Contact was made with the lower right paravertebral region, but no direct pressure was applied and there was no extension. This action was performed for 3 minutes on both sides for patients in Groups 1 and 3.

Either OMT or sham manipulative treatment was thus administered three times to all patients postsurgically: (1) approximately four hours after the patient was returned to her room from the postanesthesia care unit, (2) at approximately 8 AM the day after surgery, and (3) at approximately 2 PM on the day after surgery.

The variables of total morphine usage (patient-controlled analgesia pump and rescue) per 24-hour period, morphine blood concentration (radioimmunoassay) every 12 hours, subjective pain scores (scale: 0–10), and subjective nausea/vomiting scores (scale: 0–3) were recorded by the patient and nurse-observer every 12 hours.

Based on our study design, individual one-factor (group assignment) analysis of variance tests were performed on the results of patient morphine blood concentration levels at 24 hours, total morphine dose at 24 and 48 hours postsurgery, patient weight (kg), patient age, and length of surgery. Comparisons among randomized groups were made using the least square means from the analysis of variance. Comparisons among the four randomized groups were made using the Newman-Keuls test.

In addition to analyzing the four randomized groups from this study, two separate hypotheses were developed to assess the effect of OMT in the patients randomized to receive saline (Group 2) and those randomized to receive morphine (Group 4). Analysis of variance was used for all continuous variables. Multinomial variables (eg, subjective pain and nausea/vomiting scores) were ranked and analyzed using the analysis of variance. Any P values of less than .05 were interpreted as significant.
Results
Significant ($P<.05$) differences were found in several areas:
- Patients in Group 4 weighed more than those in any of the other three study groups (Figure 1);
- Patients in Group 4 used less total morphine than those in Group 3 from 0–24 hours postoperatively (Figure 2) and from 25–48 hours postoperatively (Figure 3);
- Morphine blood concentrations were lower at 24 hours among subjects in Group 4 compared with subjects in Group 1 (Figure 4).

No significant differences were detected among the four groups with respect to patient demographics such as age and duration of surgery. Pain and nausea/vomiting scores as recorded by patient self-report and by nurse-observer at 12, 24, 36, and 48 hours after surgery were similar among all groups.

Comment
In patients who underwent elective TAH, the use of OMT when added to preemptive IV administration of morphine improved the efficacy of patient-controlled postsurgical analgesics during the immediate 48-hour postoperative period.

During the first 24 hours after surgery, subjects who had received only preemptive morphine and postoperative sham manipulative treatment (Group 3) used 0.51 mg/kg morphine delivered by the IV patient-controlled analgesia pump, whereas those who were given preemptive morphine and postoperative OMT (Group 4) self-administered only 0.17 mg/kg morphine ($P=.02$).

In the second 24 hours (25–48 hours), more morphine was used by participants in the morphine groups (Groups 3 and 4), but the results were essentially similar: 1.14 mg/kg in the sham treatment group versus 0.42 mg/kg in the OMT group ($P=.011$).

This finding is more interesting, however, when one notes that the patients in this group (Group 4) weighed more on average than subjects in the other three groups (Figure 1) and yet they used the lowest amount of postsurgical morphine.

Although the imbalance of assignment of patients across the four groups vis-à-vis average patient weight was unintentional, this inadvertent misdistribution was not a confounding factor because data obtained regarding patient-controlled morphine use at 24 and 48 hours after surgery were normalized through the use of standard weight-dependent dosing recommendations (mg/kg).

In addition, the average blood concentration of morphine in Group 1 (saline and sham treatment) was 0.43 ng/mL at 24 hours after surgery, whereas those patients in Group 4 (morphine and OMT) had a significantly ($P=.04$) lower concentration, 0.17 ng/mL. Blood concentrations of morphine are in the format of pharmacotherapeutic drug monitoring and, as such, reflect and thus encapsulate weight and dosage as a single important parameter.

There was no difference in subjective pain scores as reported by patients and nurse-observers among the four study groups. A similar finding has been reported by Miaskowski et al.16 who showed that in treating pain from bone metastases, patients in one group required more opioid medication than the other but there was no difference between them in pain scores. Miaskowski et al16 indicated that several factors could have accounted for this disparity, including the fact that pain intensity measures may not be the most appropriate method for evaluating analgesic efficacy.

In somewhat related fashion, Adams et al17 also found no difference in pain scores while showing a reduction in pain-related parameters (concentrations of epinephrine, norepinephrine, diuretic hormone, adrenocorticotropic hormone, and cortisol) following epidural anesthesia. Epidural analgesia produced a significant decrease in concentrations of epinephrine and norepinephrine in patient sera—though other endocrine changes were less different—with no differences in subjective pain scores across study groups.

In the present study, patients remained in the hospital for at least 48 hours following major surgery. Such patients typically have many concerns beyond their respective pain—such as inability to sleep and a dislike for the meals served—which could also influence a pain report.

The uterus is supplied by numerous veins, arteries and nervous tissues, the integrity of which is compromised by uterine extraction. Viscerosomatic input from the uterus travels along pelvic splanchnic nerves to the sacral spinal cord and along visceral afferents to the dorsal horn of the thoracic 11 to lumbar 2 (T11–L2) segments. Specifically, the hypogastric nerve plexus, which carries visceral sensory fibers, is embedded within fascia surrounding the uterus and within muscular layers of the uterine wall.

With sufficient evidence of pathology, TAH may be recommended for certain patients. Furthermore, such pathology may cause visceral afferents within the hypogastric plexus to go into a state of facilitation, wherein the threshold for stimuli required to trigger nociceptive responses is lowered.

Direct injury occurring during uterine extraction may also cause neurons at the same spinal cord level to become hypersensitized to subthreshold stimuli. Therefore, postoperatively, lower thoracic and sacral regions send signals of injury, which can cause direct somatic change.

It is logical then that the lower thoracic and sacral regions would not only demonstrate somatic dysfunction but also that counterstimulation of these specific muscular regions through application of OMT would flood the same levels in the spinal cord, “distracting” the central nervous system from registering pain—and possibly preventing release of pain-sensing chemicals. Thus, the reason for terminating somatic dysfunction is because this condition causes muscular hypertonicity, presumably leading to tissue hypoxia and decreased lymph drainage and blood flow, which, in turn, impede processes that promote healing and recovery. Subjective patient pain scores would reflect such muscular hypertonicity and discomfort.
Recently, Andriesse et al.\(^{18}\) presented data from patients undergoing hysterectomy (patient responses to transient electrical stimulation of vaginal and anorectal mucosa and balloon distention of rectum) that demonstrate visceral afferents as sensitized following TAH.

The OMT protocol selected for the present investigation was designed to reduce somatic nociceptive stimuli from thoracolumbar and pelvic levels by diminishing somatic dysfunction. The levels involved may have (1) been facilitated before surgery as a result of a barrage of afferent stimuli from the underlying pathophysiology that may have prompted the need for a total abdominal hysterectomy, (2) harbored facilitated segments that are known to be the result of viscero-somatic reflexes, (3) been facilitated by afferent volleys from the surgical procedure, and/or (4) played a role in maintaining somatosomatic or somatovisceral processes associated with pain.

Osteopathic manipulative treatment, as applied to the lower thoracolumbar region (T8–L5) and the sacrum (S1–S5), can reduce specific somatic dysfunction in these areas.

In this study, sham manipulative treatment was applied to subjects unfamiliar with OMT as a treatment modality. A sham treatment group was included to help evaluate the role (or reduced importance thereof) of placebo in the perception of postoperative pain. Because touch alone (sham treatment) had no significant effect on use of patient-controlled morphine following TAH, the interpretation that OMT itself provided the additional pain relief is supported.

In a preclinical model of acute pain, morphine has been shown to prevent induction of the c-fos gene, an immediate marker of noxious stimuli in Rexed layers I, II, and V of the spinal cord.\(^{19,20}\) By diminishing surgery-induced activation of dorsal horn neurons, morphine would reduce sensitization of those neurons and thus diminish postsurgical pain.

Although a previous pilot study by Goldstein et al.\(^{7}\) showed a trend toward using preemptive morphine to improve analgesia following hysterectomy, the results were not statistically significant. When employed alone (ie, with sham treatment) in this study, preemptive morphine did not have any effect on postoperative use of patient-controlled morphine. Similarly, when OMT was administered without preemptive morphine, it also produced no significant alteration in this parameter.

Although OMT is a treatment modality frequently used to decrease pain and stress, there are no controlled studies using objective data to evaluate the effectiveness of a combination of preemptive morphine and postsurgical OMT in patients who undergo elective TAH. We conclude on the basis of this investigation that such a combination improves analgesic efficacy and patient comfort in the immediate 48-hour postoperative period following this surgical procedure.

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References