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The use of tenoxicam to prevent symptoms of discomfort induced by vagotonia during uterus manipulation in cesarean sections

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Abstract

Purpose: Symptoms such as nausea, vomiting, tightness of the chest, bradycardia, and shoulder or abdominal discomfort, caused by vagotonia occurring during uterus manipulation, have concerned healthcare professionals for some time. Patients sometimes report these symptoms when undergoing spinal anesthesia for cesarean sections (CSs). We designed a prospective, double-blind study to investigate the effectiveness of tenoxicam in preventing these symptoms of discomfort.

Methods: A total of 105 American Society of Anesthesiologists (ASA) class I-II nulliparous pregnant women, who were scheduled for a CS, were enrolled into this prospective, double-blind study. Spinal anesthesia was conducted to reach a peak dermatome level of no more than T3. The 100 patients were randomly divided into 2 groups having completed study course: Group T (N = 50) received a 20 mg dose of tenoxicam in 5 mL of normal saline (NS) immediately after skin incision and Group N (N = 50) only received 5 mL NS. The incidence and severity of the symptoms experienced by the patients were recorded by a nurse anesthetist who was blinded to the injection regimen the patients were receiving. A chi-square test was used for statistical analysis *t* test and $P < .05$ was defined as significant.

Results: The incidence and degree of severity of nausea and vomiting were same in both the groups. The incidence and degree of severity of bradycardia, nausea, vomiting, tightness of the chest, shoulder discomfort, and abdominal discomfort were lower in Group T than in Group N.

Conclusion: Tenoxicam might theoretically block the parasympathetic vagus pathway and decrease the visceral pain or visceral-specific symptoms, alleviating the symptoms caused by vagotonia. However, the prophylactic effect of tenoxicam in reducing the incidence and severity of nausea and vomiting was not statistically significant. This could be because nausea and vomiting are not solely caused by vagotonia, but also by other mechanisms.

Abbreviations: ASA = American Society of Anesthesiologists, CS = cesarean section, GI = gastrointestinal, IONV = intraoperative nausea and vomiting, NS = normal saline, NSAIDs = nonsteroidal anti-inflammatory drugs, OR = operating room, SD = standard deviation.

Keywords: cesarean section, tenoxicam, uterus manipulation, vagotonia

1. Introduction

Symptoms such as nausea, vomiting, tightness of the chest, shoulder or abdominal discomfort, or severe bradycardia[1] are commonly reported during uterus manipulation in patients undergoing spinal anesthesia for a cesarean section (CS).[2,3] These symptoms might cause significant distress to the patient and also interfere with the surgical procedure. The current medical literature has addressed the causative factors for nausea and vomiting separately, rendering it difficult for anesthesiologists to gain a comprehensive understanding of these key complications. According to the review article by Balki et al,[4] nausea and vomiting may be related to hypotension, inadequate depth of spinal anesthesia, surgical stimuli (uterus manipulation), uterotonic agents, and the inability to block visceral pain using local spinal anesthesia alone. With the exception of hypotension, the other 4 mechanisms have a high possibility to induce vagotonia.[5] Furthermore, it is known that spinal anesthesia can cause a sympathetic block, which may also be related to vagotonia.[5] Hypotension would be treated with medication perioperatively. To prevent symptoms induced by vagotonia, a higher dose of local anesthetic with opioid can be used to keep the

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spinal dermatome level above T5 throughout an entire CS. However, the use of high spinal levels (above T2) might induce significantly higher levels of hypotension and patients could suffer from breathing difficulties or profound bradycardia. Another treatment option involved sedating patients adequately using propofol or midazolam.

Previous studies have indicated that nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce pain caused by uterine cramping.[6,7] Tenoxicam is the oxicam class of NSAIDs. The characteristic of long elimination half-life (60–75 hours) and a quick onset time of within 15 minutes post-intramuscular injection is capable of once-daily administration.[8,9] For various postoperative setting, tenoxicam's property offers a potentially useful analgesic.[10,11] Many studies have shown tenoxicam to be a useful adjuvant to opioids after a CS. In our previous study,[12] we demonstrated that an intraoperative injection of 20 mg of tenoxicam was sufficient to enhance the effects of intravenous patient controlled analgesia with morphine, easing the pain of uterine cramping for the first 24 hours after a CS. In another study,[13] 40 mg of intravenous tenoxicam significantly reduced the intensity of uterine cramps without leading to further side effects.

Before conducting this prospective study, we observed 25 patients undergoing a CS. It was noted that tightness of the chest was experienced in approximately 24% of patients, and shoulder or abdominal discomfort in around 48% and 40%, respectively, during uterus manipulation. A limited prophylactic result was observed when atropine was used and an effective prophylactic result was observed in patients using tenoxicam. It was hypothesized that tenoxicam can attenuate the pain experienced from uterine contraction and manipulation, and that it can reduce the incidence and severity level of symptoms induced by vagotonia. This current study aimed to evaluate the efficacy of tenoxicam in preventing symptoms of discomfort induced by vagotonia.

2. Methods

This study was a randomized, placebo-controlled, double-blinded study, approved by the Research Ethics Committee of National Taiwan University, which was certified by the Association for the Accreditation of Human Research Protection Program in June 2008 (IRB: 200812040R). This study was conducted and completed between June 2008 and December 2008. As clinical trials were not required to be registered prior to 2009, the online registration was not completed. The first patient was enrolled in July 2008. After we received written informed consent from all patients, 105 nulliparous, pregnant women, deemed to have an American Society of Anesthesiologists (ASA) classification of I or II, who were scheduled for an elective CS, were enrolled in this study. The surgery timings (skin-to-skin) ranged from 50–70 min and all of the CS procedures were conducted by the same attending obstetrician. Patients with impaired liver or renal function, gastritis, gastric or duodenal ulcers, abnormal bleeding tendency, and those with a known allergy to salicylates or NSAIDs were excluded from the study. The 105 enrolled patients were randomly allocated to receive 1 of the regimens (Fig. 1). Each patient's regimen was noted and sealed in an envelope that was then opened by a trained nurse who was not involved in the study. This nurse then prepared the appropriate regimen, diluted to 5 mL, in identical syringes without specific drug labeling. All patients received a 1000 mL infusion of Ringer's solution prior to the spinal anesthesia. After the standard monitors were in place (electrocardiograph,

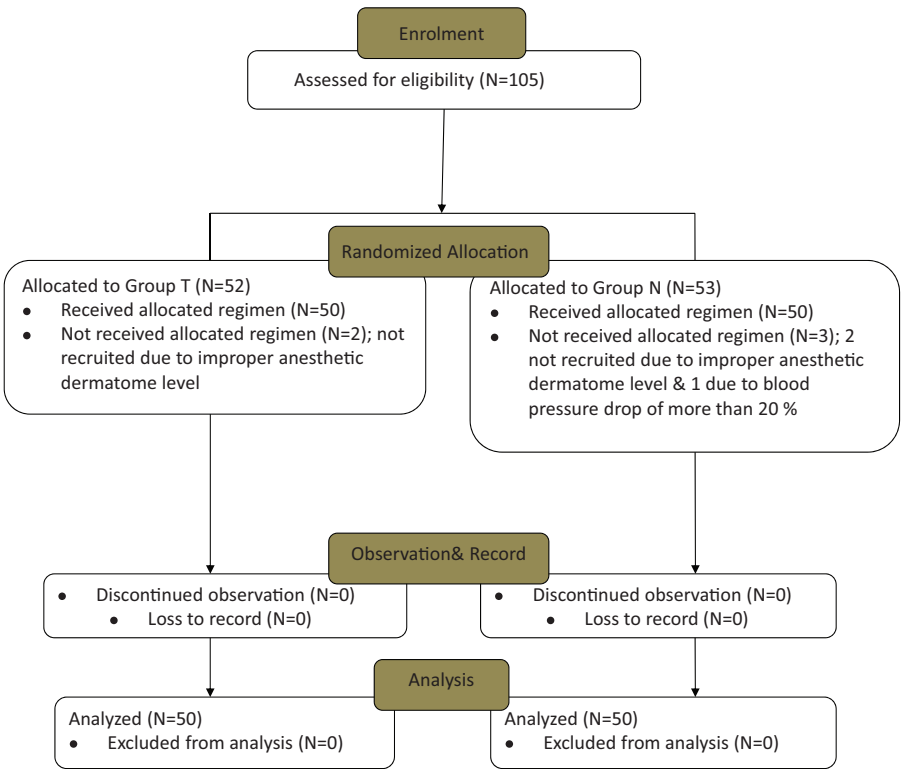

Figure 1. The CONSORT flow diagram of our participants.

automated arterial blood pressure, and pulse oximetry), the spinal anesthesia was administered using a 27-gauge Whitacre needle into the L3–4 or L4–5 interspinous space. Each patient received 9 to 12 mg of 0.5% hyperbaric bupivacaine (dosage was adjusted according to body height: 9 mg for 155 cm, 10 mg for 160 cm, and so on) for spinal anesthesia. Only patients who were found to have reached the adequate anesthetic dermatome level via pinprick testing 5 min after intrathecal injection (minimum T6, maximum T3) were recruited in this study. The 105 patients were enrolled and randomly divided into study group (Group T, N = 52) and control group (Group N, N = 53): after skin incision, Group T received a 20 mg dose of tenoxicam in 5 mL of normal saline (NS) and Group N received 5 mL NS. Four patients were excluded due to inadequate anesthetic dermatome level (above T3 or below T6), 2 from the tenoxicam group (Group T) and 2 from the NS group (Group N). Blood pressure was controlled to be within 20% of the baseline through the use of prophylaxis with intravenous hydration and 20 mg ephedrine; 1 patient from Group N was excluded due to a blood pressure drop of more than 20% (compared with baseline), who complained of severe nausea and vomiting. Group T (N = 50) received 20 mg of tenoxicam in 5 mL NS immediately after skin incision, and Group N (N = 50) received 5 mL NS alone. After the umbilical cord was clamped, 0.2 mg intravenous ergonovine and 30 units of oxytocin were administered. The incidence and severity of bradycardia, nausea (including retching), vomiting, tightness of the chest, and shoulder or abdominal discomfort were recorded by the nurse anesthetist in the operating room (OR) during the uterus manipulation and throughout the surgery. All patients, investigators (including the OR nurse anesthetist who collected the intraoperative data), and the anesthesiologists conducting spinal anesthesia were blinded to treatment the patient had received. Nausea was defined as a subjective and unpleasant sensation associated with the conscious awareness of the urge to vomit. Retching was characterized by the rhythmic and spasmodic contractions of the respiratory muscles, diaphragm, chest wall, and abdominal muscles, without the expulsion of gastric contents. Vomiting was defined as the forceful expulsion of gastric contents from the mouth, brought about by coordinated motor changes of the muscles of the respiratory and gastrointestinal (GI) systems. Tightness of the chest was defined as any type of pain or discomfort occurring between the upper stomach area and lower neck. Shoulder discomfort was defined as any type of pain or soreness around the shoulder area. Abdominal discomfort was characterized as any type of pain or ache (cramping, stretching, or dull pain) around abdominal area. Significant bradycardia was defined as a drop in heart rate of more than 20% (compared with baseline). If the patients could not tolerate the nausea or vomiting, 4 mg of ondansetron was administered to treat these symptoms, and they were defined as "severe" (needed treatment). If patients could not tolerate any chest tightness, shoulder or abdominal discomfort, they were given midazolam or propofol for treatment and they were also defined as "severe" (needed treatment). If patient suffered from severe bradycardia (a drop in heart rate of more than 40% compared with baseline), 0.4 mg atropine was administered to treat this and the case was defined as "severe" (needed treatment).

3. Statistical analysis

The primary end point was the incidence of bradycardia, nausea, vomiting, tightness of the chest, and shoulder or abdominal discomfort recorded by the OR nurse anesthetist during uterus manipulation and throughout the surgery. The secondary end points were the severity of these symptoms (i.e., needed treatment). From our preliminary study of 25 patients, the incidence and severity of these symptoms were recorded in Table 1. To obtain an 80% chance of finding a 20% decrease in the basal incidence of nausea (52%) with a 0.05 (2 tailed) level, a minimum of 47 patients were required in each group. With consideration for potential dropouts, a total of 50 patients were included in each group. Data are presented as means (standard deviation [SD]), numbers, or percentages. The Student's t test or the Mann-Whitney test was used to compare intergroup differences. The χ^2 test or Fisher's exact test was used for the categorical variables. The P values were corrected using the Bonferroni method and P values $<.05$ were considered to be statistically significant. Statistical Package for the Social Sciences (SPSS) software for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA), was used for the analysis.

4. Results

Figure 1 is the CONSORT flow diagram of our participants. A total of 105 patients were screened, and randomly assigned into 1 of the 2 groups (52 in Group T and 53 in Group N). Four patients were excluded due to improper anesthetic dermatome level (above T3 or below T6), 2 from Group T and 2 from Group N. One patient in Group N was excluded due to the blood pressure dropping more than 20%, compared with baseline (Fig. 1). The incidence and severity of symptoms noted during our preliminary observation on 25 patients are shown in Table 1. Table 2 displays the baseline parturient characteristics of the 2 groups; no significant differences were noted between the 2 groups with regard to age, weight, height, body mass index, parity, ASA classification, and surgery timing. Table 3 shows the incidence of discomfort symptoms induced by vagotonia in patients in both groups. There were no significant differences observed with regard to the incidence of nausea and vomiting between 2 groups ($P > .05$). Conversely, the incidences of bradycardia, chest tightness, and shoulder or abdominal discomfort were significantly lower in Group T than Group N. The severity of these vagotonia-induced symptoms is shown in Table 4. This difference between Group T and Group N indicates that the prophylactic efficacy of tenoxicam is truly significant. In Group T, only 1 patient needed treatment for chest tightness and another patient needed treatment for abdominal discomfort. In Group N, 2 patients experiencing bradycardia, 4 with chest tightness, 6 with abdominal discomfort, and 6 patients with shoulder discomfort needed treatment.

Table 1

The incidence of discomfort symptoms induced by vagotonia from preliminary observation on 25 patients.

Symptom and sign	Observation on 25 patients (%)	Need for treatment (%)
Bradycardia*	12 (3/25)	4 (1/25)
Nausea	52 (13/25)	12 (3/25)
Vomiting	28 (7/25)	8 (2/25)
Chest tightness	24 (6/25)	8 (2/25)
Shoulder discomfort	48 (12/25)	12 (3/25)
Abdominal discomfort	40 (10/25)	12 (3/25)

* Bradycardia is defined as heart rate dropping >20% of baseline.

Table 2

Baseline parturient characteristics.

	Group T (n = 50)	Group N (n = 50)	*P* value
Age	32.3 (2.71)	32.7 (2.68)	>.05
Height (cm)	159.1 (3.31)	160.3 (3.86)	>.05
Weight (kg)	68.5 (3.65)	69.1 (4.69)	>.05
BMI (kg/m^2)	27.1.0 (1.46)	26.9 (1.76)	>.05
GA (weeks)	38.5 (0.8)	38.7 (0.71)	>.05
ASA class I	28 (56%)	27 (54%)	>.05
ASA class II	22 (44%)	23 (46%)	>.05
Operation time (min)	60.6 (3.67)	61.2 (3.64)	

Data presented as mean (SD) or number (proportion).

ASA = American Society of Anesthesiologists, BMI = body mass index, GA = gestational age.

Table 3

The incidence of discomfort symptoms induced by vagotonia in Group T and Group N.

Symptom and sign	Group T (50)	Group N (50)	*P* value
Bradycardia*	2% (1/50)	12% (6/50)	<.05
Nausea	40% (20/50)	48% (24/50)	>.05
Vomiting	24% (12/50)	32% (16/50)	>.05
Chest tightness	6% (3/50)	26% (13/50)	<.05
Shoulder discomfort	8% (4/50)	44% (22/50)	<.05
Abdominal discomfort	10% (5/50)	36% (18/50)	<.05

* Bradycardia is defined as heart rate dropping >20% from baseline.

5. Discussion

Vagotonia is defined as the pathological overactivity, or irritability, of the vagus nerve, which adversely affects the function of the blood vessels, stomach, and innervated muscle; it can also be referred to as sympathetic imbalance.[14] Previously, during CSs, some obstetricians would suture the uterus without first pulling the uterus out of abdominal cavity. Currently, most obstetricians prefer to pull the uterus out of abdominal cavity before suturing, not only for convenience and ease, but also because it is much safer, as it allows one to check for bleeding risks for preventing postpartum hemorrhage.[15–17] When obstetricians pull out and manipulate the uterus, there is an increased risk of inducing vagotonia through 1 of the 2 mechanisms: direct surgical stimulation inducing overactivity or irritability of the vagus nerve; or uterus contraction induced by drugs (30 units of oxytocin postdelivery). During the manipulation of the uterus, symptoms of discomfort, such as tightness of the chest, shoulder or abdominal discomfort, or even severe bradycardia,[1] may be the direct result of vagotonia. Thus, if some prophylactic method to reduce the impact of vagotonia during uterus manipulation could be identified, there would be fewer patients suffering from the occurrence and severity of these uncomfortable sensations during such obstetric procedures. Furthermore, this would eliminate the need for any medication to treat these individual discomfort symptoms. However, there may be 2 different mechanisms (including both anesthetic and nonanesthetic factors) by which intraoperative nausea and vomiting (IONV) is induced after the administration of regional anesthesia for CSs, and these should be clearly differentiated, to allow for appropriate prophylactic and therapeutic management.[18] IONV is best prevented by controlling hypotension, optimizing the use of neuraxial and intravenous opioids, improving the quality of the block, minimizing the surgical stimuli, and through judicious administration of uterotonic agents.[19] Thus, even though preventative measures were taken to reduce the vagotonia impact during uterus manipulation in this study, there were still a few patients who suffered from IONV and needed medication treatment.

Spinal anesthesia using local anesthetics and opioids is widely used among obstetric patients undergoing a CS. In a previous study,[20] some obstetric anesthesiologists indicated their desire to use a full dose of intrathecal local anesthetic (around 15 mg hyperbaric bupivacaine) with an opioid to keep their patients' spinal dermatome level above T5 throughout the whole CS procedure (inclusive of the uterus manipulation period).[21] However, a high spinal dermatome level (above T2) might induce significantly higher levels of hypotension and the patient could suffer from breathing difficulties, or even profound bradycardia.[22] Nevertheless, it is known that if a high spinal dermatome level (above T5) is achieved throughout the whole CS procedure, then the incidence and severity of vagotonia-induced discomfort symptoms could be significantly reduced.[23] Most anesthesiologists,[24,25] including those at the National Taiwan University Hospital, would not use a full dose of intrathecal local anesthetic; most routinely used a standard dose which is adjusted according to body height, 9 mg for 155 cm, 10 mg for 160 cm, and so on. Thus, the dermatome level of our patients could drop below T5 during uterus manipulation. The data from our preliminary study on 25 patients (shown in Table 1) indicated that the incidence and severity of vagotonia-induced discomfort symptoms could be highly significant and may be perplexing to obstetricians and anesthesiologists. In this study, there were a few patients who could not tolerate their symptoms of chest tightness and shoulder or abdominal discomfort, and in these cases we had no choice but to use midazolam or propofol to sedate them and alleviate their symptoms. If patients suffered from severe bradycardia, they would be prescribed 0.4 mg atropine as treatment. However, skin-to-skin contact between the mother and infant during a CS has become increasingly popular. If the patient was sedated, it would be impossible to keep the mother lucid and for the first skin-to-skin contact to take place, once the infant was delivered.

Table 4

The severity of discomfort symptoms induced by vagotonia in Group T and Group N.

Symptom and sign	Group T (50)	Group N (50)	*P* value
Bradycardia			
Need for treatment (>40%)	0% (0/50)	4% (2/50)	<.05
No need for treatment (<40%)	2% (1/50)	8% (4/50)	<.05
Nausea			
Need for treatment	12% (6/50)	16% (8/50)	>.05
No need for treatment	28% (14/50)	32% (16/50)	>.05
Vomiting			
Need for treatment	4% (2/50)	6% (3/50)	>.05
No need for treatment	20% (10/50)	26% (13/50)	>.05
Chest tightness			
Need for treatment	2% (1/50)	8% (4/50)	<.05
No need for treatment	4% (2/50)	18% (9/50)	<.05
Shoulder discomfort			
Need for treatment	0% (0/50)	12% (6/50)	<.05
No need for treatment	8% (4/50)	32% (16/50)	<.05
Abdominal discomfort			
Need for treatment	2% (1/50)	12% (6/50)	<.05
No need for treatment	8% (4/50)	24% (12/50)	<.05

Thus, keeping the mother awake while providing effective prophylactic treatment to reduce the impact of vagotonia during uterus manipulation may become a key issue when conducting CS spinal anesthesia.

In our pilot study, we thought that atropine could be the optimal drug to alleviate vagotonia-induced symptoms during uterus manipulation in the course of a CS. However, the prophylactic effect of atropine was noted to be limited. Tenoxicam was then selected, with significant effect. We hypothesized that there could an association between uterus contraction and vagotonia, as well as an association between surgical stimuli and vagotonia, during uterus manipulation.[3,26,27] The contractions of the uterus may induce the production of several chemical nociceptive mediators, such as bradykinins, leukotrienes, prostaglandins, serotonin, lactic acid, and substance P.[28] This mechanism might be mediated by a secondary messenger-prostaglandin system[29] that can be inhibited by aspirin-type anti-inflammatory analgesics. In our previous study,[12] we evaluated the various analgesic effects of tenoxicam on wound pain and pain induced by uterine cramping following a CS, and concluded that an intraoperative injection of 20 mg tenoxicam was sufficient to enhance the effect of intravenous patient controlled analgesia with morphine on uterine cramping pain for the first 24 hours post-CS. In another study,[13] we aimed to investigate the effectiveness of tenoxicam in reducing the pain from uterine contractions, and concluded that 40 mg intravenous tenoxicam significantly reduced the intensity of uterine cramps in CS patients without increasing the number of side effects. With our theoretically sound hypothesis and previous experience, we conducted this prospective, randomized, double-blind, placebo-controlled study to evaluate the efficacy of tenoxicam in easing the symptoms of discomfort induced by vagotonia during uterus manipulation. Tenoxicam treatment might significantly reduce the incidence and severity of chest tightness, bradycardia, and shoulder or abdominal discomfort induced by vagotonia during uterus manipulation. However, the prophylactic effect of tenoxicam on nausea and vomiting may not be as significant, perhaps due to other mechanisms contributing to the root cause of the nausea and vomiting.

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