Delayed postoperative gastric emptying following intrathecal morphine and intrathecal bupivacaine

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Purpose: A decrease in the rate of gastric emptying can delay resumption of enteral feeding, alter bioavailability of orally administered drugs, and result in larger residual gastric volumes, increasing the risk of nausea and vomiting. We compared the effects of 1) intrathecal bupivacaine (17.5 mg) and 2) the combination of intrathecal morphine (0.6 mg) and intrathecal bupivacaine (17.5 mg) on the rate of gastric emptying in patients undergoing elective hip arthroplasty.

Methods: Twenty four fasting ASA 1-3 patients were randomly assigned, in a double blind manner, to receive intrathecal hyperbaric bupivacaine (17.5 mg), either alone (group 1), or followed by intrathecal morphine (0.6 mg) (group 2). Gastric emptying was measured (using an acetaminophen absorption technique), twice in each patient; pre-operatively, and approximately one hour postoperatively. Gastric emptying parameters are: AUC (area under the plasma acetaminophen concentration time curve), maximum plasma acetaminophen concentration (C_{max}), and time to C_{max} (tC_{max}), analyzed using paired Student's *t* tests.

Results: Gastric emptying rates were reduced in both group 1 ($AUC=14.98$ (3.8) and 11.05 (4.6) pre- and post-operatively, respectively) and group 2 ($AUC=13.93$ (3.59) and 6.4 (3.42) pre- and postoperatively, respectively); the magnitude of the reduction was greater in group 2 (AUC ($P=0.04$), C_{max} ($P=0.05$), tC_{max} ($P=0.13$)).

Conclusion: The combination of intrathecal morphine (0.6 mg) and intrathecal bupivacaine (17.5 mg) delays gastric emptying postoperatively.

Objectif : Une réduction de la vitesse de vidange gastrique peut retarder la reprise de l'alimentation entérale, modifier la biodisponibilité des médicaments administrés oralement et provoquer de plus grands volumes gastriques résiduels, ce qui peut accroître le risque de nausées et de vomissements. Nous avons comparé les effets de 1) la bupivacaine intrathécale (17,5 mg) et 2) la combinaison de morphine intrathécale (0,6 mg) et de bupivacaine intrathécale (17,5 mg) sur la vitesse de vidange gastrique chez des patients qui subissent une arthroplastie de la hanche.

Méthode : Vingt-quatre patients à jeun, ASA 1-3, ont été répartis au hasard et en double aveugle. Ils ont reçu de la bupivacaine hyperbare intrathécale (17,5 mg), soit seule (groupe 1), soit suivie de morphine intrathécale (0,6 mg, groupe 2). L'évacuation gastrique a été mesurée à deux reprises (selon la technique d'absorption de l'acétaminophène), avant l'opération et environ une heure après. Les paramètres étaient : l'aire sous la courbe (ASC) de la concentration plasmatique d'acétaminophène en fonction du temps, la concentration plasmatique maximale d'acétaminophène (C_{max}) et le temps auquel on observe la concentration maximale (tC_{max}), analysés au moyen des tests *t* de Student pour des échantillons appariés.

Résultats : Les vitesses de vidange gastrique ont été réduites chez les patients des deux groupes; 1 ($ASC=14,98$ (3,8) et $11,05$ (4,6) avant et après l'opération, respectivement) et 2 ($ASC=13,93$ (3,59) et $6,4$ (3,42) avant et après l'opération); l'importance de la réduction a été plus grande dans le groupe 2 (ASC ($P=0,04$), C_{max} ($P=0,05$), tC_{max} ($P=0,13$)).

Conclusion : La morphine intrathécale (0,6 mg) et la bupivacaine intrathécale (17,5 mg) retardent la vidange gastrique postopératoire.

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DELAYED gastric emptying occurring in the perioperative period can result in larger residual gastric volumes, increasing the risk of nausea and vomiting,¹ a delay in postoperative resumption of enteral feeding¹ and an alteration of bioavailability of orally administered drugs.²

Drugs administered intrathecally can alter the rate of gastric emptying.³ It has been demonstrated recently that intrathecal fentanyl (25 µg) delays gastric emptying during labour.³ To date, the effect of intrathecal morphine on gastric emptying in the perioperative period has not been studied. Although local anaesthetics administered epidurally have minimal effects on the rate of gastric emptying,⁴ their effects, when administered intrathecally, have not been evaluated. The aim of this study was to compare the effects of intrathecal bupivacaine (17.5 mg) alone, and the combination of intrathecal bupivacaine (17.5 mg) and intrathecal morphine (0.6 mg) on the rate of gastric emptying in patients undergoing hip arthroplasty.

Methods

With prospective institutional ethical approval, and having obtained written informed consent, 24 fasting ASA 1-3 patients scheduled to undergo hip arthroplasty were studied. Exclusion criteria included contraindications to spinal anesthesia (systemic or local sepsis, coagulopathy), gastrointestinal pathology, diabetes mellitus, previous gastric or duodenal surgery, recent (one month) surgery, any medication known to influence gastric emptying, and previous adverse reaction to morphine or bupivacaine. Patients were randomly assigned to receive either intrathecal hyperbaric bupivacaine (17.5 mg) (group 1), or intrathecal hyperbaric bupivacaine (17.5 mg) followed by intrathecal morphine (0.6 mg) (group 2). A random numbers table was used to determine allocation to group 1 or 2. Cards indicating allocations were placed in serially numbered, sealed, opaque envelopes. Both the patient and the investigator performing the measurement of gastric emptying and scoring nausea, pruritus and pain, were unaware of the group to which each patient belonged.

The rate of gastric emptying was measured on two occasions in each patient. First, it was measured on the day before surgery, having fasted from food and liquids for at least four hours, and second, approximately one hour postoperatively. Each measurement was undertaken with the patient in the semi-recumbent position.⁵ Gastric emptying was measured using an acetaminophen absorption technique.⁶ An intravenous cannula was placed in the arm contralateral to the intravenous infusion for blood sampling. Following

withdrawal of a baseline venous blood sample (4 ml), each patient ingested soluble acetaminophen (1.5G in 50 ml water). Venous blood samples were withdrawn at 10, 20, 30, 40, 50, 60, 70 and 90 min later.

The samples were centrifuged and plasma acetaminophen concentration measured, using an enzymatic colorimetric assay (Cambridge Life Sciences, Cambridgeshire, CB7 4DT, England).⁷ The method is based on the use of an enzyme specific for the amide bond of acylated aromatic amines. It cleaves the acetaminophen molecule, yielding p-aminophenol, which reacts specifically with o-cresol in ammoniacal copper solution to produce a blue color. The acetaminophen assay is specific for the parent compound and does not detect acetaminophen metabolites.⁸ At a concentration of 0.45 mmol·l⁻¹ and a standard deviation of 0.005 mmol·l⁻¹, the intra assay coefficient of variation is 1.0%; and the inter assay coefficient of variation 1.1%.⁷ The sensitivity, defined as two standard deviations from zero, is 0.01 mmol·l⁻¹.⁷ In terms of sensitivity, linearity, precision and accuracy, the enzymic assay is similar to established methods of analysis (high pressure liquid chromatography and gas chromatography) over the range 0-2.5 mmol·l⁻¹.⁸

The measures of gastric emptying used were area under the plasma acetaminophen time curve (AUC) (calculated using the trapezoidal rule), maximum plasma acetaminophen concentration attained (C_{max}), and time taken to achieve C_{max} (tC_{max}).

Immediately preoperatively, with standard monitors in place (Datex AS 3, Datex-Engstrom Ltd, Helsinki, Finland), having secured intravenous access, and placed the patient in the lateral position (operative side dependant), a 25G spinal needle was inserted at the L₃₋₄ level under aseptic conditions. Patients were not made aware whether one or two injections were made once the spinal needle had been inserted; the anesthesiologist who performed the intrathecal injection did not participate in the evaluation of the patients or estimation of gastric emptying. When freely flowing cerebrospinal fluid was identified, 3.5 ml hyperbaric bupivacaine 0.5% were injected followed by no injection (group 1), or preservative free morphine (0.6 mg) (group 2). During the operation, midazolam (up to 0.1 mg·kg⁻¹) was administered as clinically indicated. No systemic opioids were administered. The study period was designated from immediately before the intrathecal injection(s) (Time 0) until measurement of postoperative rate of gastric emptying was complete. At hourly intervals during the study period, pruritus, nausea and vomiting were assessed, and respiratory rate counted. Pruritus, nausea and vomiting were rated as absent, mild, if the

patient only reported the symptom on questioning, moderate if the symptom necessitated and responded to treatment (10 mg diphenhydramine, 4 mg ondansetron, *iv*, for pruritus and nausea, respectively) or severe if the symptom did not respond to initial treatment. Pain was assessed (Visual Analogue Scale: 0 signified no pain and 10 signified the worst pain imaginable) at one hourly intervals after intrathecal injection. If the patient was asleep, pain was assigned a 0 value, and pruritus, nausea and vomiting were rated absent. A respiratory rate <10-min was interpreted as respiratory depression.

Paired Student's *t* tests were used to compare preoperative and postoperative parameters of gastric emptying (Table II); between group parametric data were compared using unpaired Student's *t* tests (Tables I, III). Non-parametric data were analyzed using Fisher's Exact test (Tables I, III). Statistical significance was accepted at the probability level of < 0.05.

In a previous study, a similar dose of acetaminophen in a similar volume of water (1.5G in 50 ml) was administered, and it was demonstrated that intramuscular morphine (10 mg) decreased AUC by 59%.⁹ There is no evidence on which a clinically relevant change in AUC can be defined. In the absence of such evidence, we considered that a reduction in AUC by a test drug of 50% would be a clinically relevant difference. To detect this reduction, with a power of 0.9 and *P* = 0.05, eight patients in each group were required.

Results

Twenty seven patients were recruited to the study. Two patients were subsequently excluded due to inadequate spinal anesthesia; another was withdrawn due to vomiting following ingestion of acetaminophen during the postoperative measurement. Data were obtained from 24 patients. The groups were similar in terms of age, body mass index (BMI), sex, interval between drug administration and commencement of measurement of gastric emptying, duration of surgery, and the doses of ephedrine and midazolam administered (Table I). Preoperative parameters of gastric emptying {AUC (*P* = 0.53), C_{max} (*P* = 0.27), tC_{max} (*P* = 0.40)} were similar in the two groups (Table II).

One patient in group 1 complained of pain (*P*=NS) but declined treatment, and one patient in group 2 complained of nausea (*P*=NS), and was treated with ondansetron 4 mg intravenously (Table III); both patients remained in the study. Four patients in group 2 complained of pruritus (*P* = 0.26) (Table III). Two of 15 patients in group 2 developed respiratory depression on one occasion each, at Times 2 and 3, defined as a respiratory rate < 10 breaths·min; mean

TABLE I Comparison of patient characteristics, midazolam and ephedrine requirements, and interval between drug administration and commencement of gastric emptying measurement in groups 1 and 2. Data are mean ± SD or range [].

	Bupivacaine (group 1) (n=9)	Bupivacaine/ morphine (group 2) (n=15)	<i>P</i> value
Age (yr)	66.6 ± 6.54	71.1 ± 10.17	0.25
Body mass index (kg·m ⁻²)	27.2 ± 4.6	25.1 ± 3.56	0.23
Sex (f/m)	4/5	6/9	0.97
Midazolam dose (mg)	2.5 ± 2.0	2.0 ± 1.8	0.32
Ephedrine dose (mg)	0 ± 0	2.6 ± 4.6	0.21
Intrathecal drug administration-commencement of gastric emptying measurement interval (min)	119.1 ± 19.5 [90-150]	121.2 ± 40.4 [75-215]	0.88

TABLE II Comparison of preoperative and postoperative gastric emptying parameters {area under plasma acetaminophen concentration time curve (AUC), maximum plasma acetaminophen concentration (C_{max}), and time taken to attain C_{max} (tC_{max})} in groups 1 and 2.

Data are mean ± SD.

	AUC (mmol·l ⁻¹ ·min)	C _{max} (mmol·l ⁻¹)	tC _{max} (min)
Bupivacaine (Group 1)			
Preoperative n=9	14.98 ± 3.8	0.25 ± 0.06	30.55 ± 20.7
Postoperative n=9	11.05* ± 4.6	0.20 ± 0.13	44.44 ± 27.4
Bupivacaine/Morphine (Group 2)			
Preoperative n=15	13.93 ± 3.59	0.23 ± 0.06	39.0 ± 24.9
Postoperative n=15	6.40* ± 3.42	0.11* ± 0.05	39.1 ± 26.9

* *P* < 0.05 compared with preoperative value.

respiratory rate was similar in the groups (*P*=NS) (Table III).

In group 1, the rate of gastric emptying, as quantified by AUC, was less before, than after surgery (*P* = 0.02); C_{max} (*P* = 0.17) and tC_{max} (*P* = 0.17) displayed a trend towards delayed gastric emptying that did not achieve statistical significance (Table II). In group 2, the rate of gastric emptying was less postoperatively, than preoperatively, as quantified by AUC (*P* < 0.0001), and C_{max} (*P* < 0.0001); tC_{max} was similar pre- and postoperatively (Table II). The magnitude of the reduction in the rate of gastric emptying was greater in group 2 than in group 1 {AUC (*P* = 0.04), C_{max} (*P* = 0.05), tC_{max} (*P* = 0.13)}.

Discussion

Our results demonstrate that the rate of gastric emptying of liquids is reduced following the intrathecal administration of hyperbaric bupivacaine (17.5 mg) alone, and when combined with intrathecal morphine (0.6 mg). The magnitude of the reduction in the rate of gastric emptying was greater in the patients who received intrathecal morphine.

Animals who have received intrathecal morphine demonstrate a dose dependent inhibition of small bowel transit.¹⁰ In labouring women receiving epidural bupivacaine, the addition of intrathecal fentanyl (25 µg), compared with epidural fentanyl (50 µg), delayed gastric emptying of liquids.³ However, active labour itself may delay gastric emptying.¹¹ Our study sample represents an homogenous group of adult non-pregnant patients undergoing elective surgery, uniform in nature and duration. In a study of 20 male volunteers, propagation velocity of the duodenal phase 3 migrating motor complex (MMC), a measure of gastrointestinal motor activity, was reduced following administration of intrathecal morphine (0.4 mg).¹² This study also demonstrated retrograde movement of the MMC and increased pressures in the duodenum. In the same study, changes in the rate of gastric emptying, using an acetaminophen absorption technique, were measured. In the absence of a control group, no conclusion could be made concerning the independent effect of intrathecal morphine on the rate of gastric emptying. As rates of gastric emptying are subject to considerable inter-subject variability,¹³ we used within-patient comparisons, with the patients acting as their own controls. To date, because the effects of intrathecal morphine on perioperative gastric emptying have not been studied, we demonstrated that intrathecal morphine (0.6 mg) delays gastric emptying in the immediate postoperative period.

There are three sites at which intrathecal opioids may exert their effects on gastrointestinal motility; opioid receptors in the myenteric plexus of the stomach, the spinal cord, and the brain. Gastric emptying

is delayed by injection of opioids into the arterial supply of the stomach,¹⁴ and by intraperitoneal administration.¹⁵ Methylnaltrexone, an opioid antagonist which does not cross the blood brain barrier, prevents opioid mediated delay in gastrointestinal transit.¹⁶ These findings support a local mechanism. If this is so, a peripherally acting opioid antagonist, such as methylnaltrexone, may prove clinically useful in maintaining normal gastric motility in the perioperative period. Porreca *et al.* demonstrated that opioid induced delay in gastrointestinal transit was mediated at spinal cord level by both delta and mu receptors, while being mediated exclusively by mu receptors at supraspinal level.¹⁷ Furthermore, intrathecal morphine inhibited gastrointestinal transit in spinal cord transected mice, indicating that the effect can occur at the level of the spinal cord, without rostral spread via cerebrospinal fluid, and without involvement of possible ascending pathways.¹⁰ However, opioids also appear to act centrally; gastric emptying is delayed by intracerebral administration of opioids in doses too small to be effective peripherally.¹⁷

In our study, patients receiving intrathecal bupivacaine as a single agent (group 1) demonstrated a reduction in the rate of gastric emptying. These patients underwent both local anesthetic mediated sympathectomy and hip arthroplasty. Adrenergic inhibition accelerates the rate of gastric emptying;¹⁸ local anesthetic mediated sympathectomy would therefore be expected to increase the rate of gastric emptying.

Previous investigators demonstrated that there was no change in the rate of gastric emptying following epidural bupivacaine-mediated sympathectomy, both in volunteers not undergoing surgery,⁴ and in patients undergoing minor lower limb surgery.¹⁹ Following abdominal hysterectomy under bupivacaine-induced epidural anesthesia, the rate of gastric emptying was delayed.²⁰ The differing results of these studies may be due to the influence of the surgery itself, which can inhibit gastrointestinal motility through reflex activa-

TABLE III Mean respiratory rate and number of patients complaining of pruritus, nausea, and pain in groups 1 and 2, at hourly intervals following drug administration.

Time (hr)	Bupivacaine (group 1)					Bupivacaine and morphine (group 2)				
	0 (N=9)	1 (n=9)	2 (n=9)	3 (n=9)	4 (n=1)	0 (n=15)	1 (n=15)	2 (n=15)	3 (n=13)	4 (n=5)
Pruritus	0	0	0	0	0	0	0	4	2	2
Nausea	0	0	0	0	0	0	0	0	1	0
Pain	0	0	0	1	0	0	0	0	0	0
Respiratory Rate (breaths·min ⁻¹)	13.5	13.5	14.4	14	18	14.2	14.7	15	14.7	14.4

tion of sympathoadrenergic inhibitory pathways.¹⁸ In our study, we did not employ formal testing of the extent of the sensory blockade during measurement of the rate of gastric emptying. A previous study demonstrated that epidural bupivacaine-induced sensory blockade, extending above and below the levels at which gastric innervation occur (T_{6-10}), did not alter the rate of gastric emptying.⁴ The reduction in the rate of gastric emptying seen in group 1 may be due to the effects of the intrathecal bupivacaine, the surgery, or a combination of these factors.

Unwanted effects of intrathecal opioids include pruritus, nausea and respiratory depression.²¹ Previous studies have reported the incidence of pruritus following epidural morphine to range up to 100%, and the incidence of nausea to range from 12-50%.²¹ Pruritus occurred in four of 15 patients in group 2, and did not occur in any patients in group 1; this difference did not achieve statistical significance ($P = 0.13$). The lack of a difference in the incidence of pruritus in the two groups may be due to the small number of patients studied. Alternatively, as the incidence and severity of pruritus is dose dependent,²¹ a dose of 0.6 mg morphine may not increase the occurrence of pruritus. In our study, only one of 24 patients complained of nausea. A previous study of 10 volunteers receiving intrathecal morphine (0.4 mg) concluded that the onset of nausea and vomiting occurred between 228-684 min following its administration.¹² In our study, assessment of nausea scores was completed in all patients by 240 min following intrathecal drug administration. Onset of nausea may, therefore, have occurred after the study period, resulting in an underestimation of the true incidence. Two patients in group 2 developed respiratory depression (respiratory rate $< 10 \cdot \text{min}^{-1}$). No patient required administration of naloxone or ventilatory support. The incidence of respiratory depression increases with age, and characteristically occurs from six to ten hours later,²¹ necessitating close monitoring.

Potential confounding factors which have been shown to influence gastric motility include phase of menstrual cycle,²² circadian variation,²³ age,²⁴ and posture.⁵ In this study, no attempt was made to take account of the first two factors, because the effect of both has been shown not to apply to gastric emptying of liquids.^{22,23} Gastric emptying of liquids, although slightly slower in the elderly {77 (range 70-84) yr}, lies within the normal range for young adults {34 (range 21-63) yr}; the ages of the patients studied were intermediate between these two ranges, and were similar in the two groups (Table I). The effect of posture on gastric emptying did not influence our

results because all patients were studied in the semi-recumbent position.

The acetaminophen absorption technique used in this study is an accurate measure of the rate of gastric emptying of liquids, but not solids.⁶ Because separate mechanisms govern these two processes, our conclusions refer only to the former.

Delayed gastric emptying alters bioavailability of orally administered drugs.² This has implications for the perioperative administration of oral analgesics, antibiotics and medications controlling concurrent disease, such as hypertension and epilepsy. Delayed gastric emptying may result in larger residual gastric volumes, increasing the risk of pulmonary aspiration of gastric contents at induction of anesthesia. Postoperative resumption of enteral feeding may be delayed, and the incidence of nausea and vomiting increased.

In conclusion, intrathecal administration of morphine (0.6 mg) and bupivacaine (17.5 mg), is associated with a delay in the rate of gastric emptying of liquids in the postoperative period. The magnitude of the reduction is greater following both morphine (0.6 mg) and bupivacaine (17.5 mg) than when bupivacaine alone is administered.

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