Improved bowel function after gynecological surgery with epidural bupivacaine-fentanyl than bupivacaine-morphine infusion

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Purpose: To compare postoperative gastrointestinal recovery between continuous epidural bupivacaine-fentanyl and bupivacaine-morphine.

Methods: In a blinded, randomized, prospective trial, 60 women undergoing surgery for gynecologic cancer were studied. Anesthesia was provided by a combined general/epidural (L_{2-3} catheter) technique without epidural opioids. Postoperative epidural analgesia was by continuous infusion of bupivacaine 0.1% with either morphine 0.05mg·ml^{-1} (BM) or fentanyl 5 μg·ml^{-1} (BF). Visual Analogue Scale (VAS) scores for pain at rest and during movement, and the return of bowel function were collected for three days and the duration of hospitalization were noted.

Results: On POD-1, 18.5% of patients in the BM group had emesis compared with none in the BF group (P = 0.038) and fewer patients in the BM group tolerated clear oral fluids (11.1% BM *vs* 40.6% BF, P = 0.025). These differences became insignificant on POD-2 and 3. Median pain scores were comparable at rest and ranged from 10-20 in the BM group *vs* 0-20 in the BF group over the three days. Similarly, median pain scores with movement respectively ranged from 20-25 and 20-30 in the BF and BM groups. The mean duration of hospitalization was longer in the BM group (5.7 ± 2.4) *vs* BF (4.5 ± 1.2 days), P = 0.017.

Conclusion: Epidural BM and BF provided equally effective postoperative analgesia at rest and during movement. Compared with BM, epidural BF is associated with less emesis and an increased ability to tolerate oral fluids on POD-1 and an overall shorter hospital stay.

Objectif : Comparer la récupération gastro-intestinale postopératoire à la suite d'une perfusion péridurale continue avec bupivacaïne et, fentanyl ou morphine.

Méthode : L'étude à l'insu, randomisée et prospective a porté sur 60 femmes qui ont subi l'opération d'un cancer gynécologique. Une technique générale/péridurale combinée (cathéter dans l'espace L_{2-3}) sans opioïdes périduraux a permis l'anesthésie. L'analgésie péridurale postopératoire comprenait une perfusion continue de bupivacaïne à 0,1 % avec, soit 0,05mg·ml^{-1} de morphine (BM), soit 5μg·ml^{-1} de fentanyl (BF). On a enregistré pendant 3 jrs les scores de douleur au repos et pendant le mouvement à l'échelle visuelle analogique (EVA), et le retour de la fonction intestinale. La durée de l'hospitalisation a été notée.

Résultats : Au jour 1 postopératoire, 18,5 % des patientes du groupe BM avaient des vomissements mais aucune du groupe BF (P = 0,038) et peu de patientes du groupe BM ont toléré les liquides oraux clairs (11,1 % BM *vs* 40,6 % BF, P = 0,025). Ces différences n'étaient plus significatives aux jours 2 et 3. Les scores moyens de douleur ont été comparables au repos et allaient de 10-20 pour le groupe BM*vs* 0-20 pour le groupe BF au cours des trois jours. De même, les scores moyens de douleur au mouvement se retrouvaient respectivement de 20-25 et de 20-30 pour les groupes BF et BM. La durée moyenne d'hospitalisation a été plus longue dans le groupe BM (5,7± 2,4) *vs* le groupe BF (4,5 ± 1,2 jours), P = 0,017.

Conclusion : L'analgésie péridurale BM et l'analgésie BF ont fourni un soulagement équivalent de la douleur postopératoire au repos et lors de mouvements. L'analgésie avec BF, comparée à l'analgésie avec BM, est associée à moins de vomissement et à une capacité accrue de tolérance aux liquides oraux le premier jour postopératoire ainsi qu'à un séjour hospitalier plus court.

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EPIDURAL analgesia has become popular for the management of postoperative analgesia following abdominal surgery. Controversy surrounds the effects of epidural opioids on the gastrointestinal (GI) tract. Liu *et al.* have shown that an infusion of epidural bupivacaine and morphine is associated with a shorter duration of postoperative ileus.[1] On the other hand, Thoren *et al.* have shown that epidural morphine prolongs postoperative ileus.[2,3]

Morphine, because of its ionized hydrophilic nature, undergoes slower elimination from the neural axis, spreads more rostrally, and has a tendency to produce more side-effects than does fentanyl.[4] In this randomized, blinded, prospective study, we compared the efficacy of two postoperative analgesic regimens: epidural bupivacaine-morphine mixture (BM) and epidural bupivacaine-fentanyl mixture (BF) with respect to VAS pain scores at rest and during movement, return of bowel function and duration of hospitalization.

Methods

Following local investigational review board approval, informed written consent was obtained from 60 women, ASA physical status 1 to 3, undergoing major abdominal surgery for ovarian, cervical or uterine cancer. Women undergoing a bowel resection were excluded from the study.

Patients were randomly assigned using a random number generated computer program to receive either a continuous epidural infusion of bupivacaine 0.1% with 0.05 mg·ml^{-1} morphine, (BM group) or a continuous epidural infusion of bupivacaine 0.1% with 5 μg·ml^{-1} fentanyl, (BF group).

A standardized clinical pathway (SCP) protocol for managing gyne-oncologic surgical patients was employed during the study. The SCP has specific guidelines for preoperative assessment, intraoperative management, postoperative management and discharge criteria covering the entire hospitalization.

In accordance with the SCP guideline, the BM and BF groups preoperatively received a lumbar (L_{2-3}) epidural catheter inserted 4 cm cephalad into the epidural space. After negative aspiration, a test dose of 3 ml lidocaine 1.5% containing 15 μg epinephrine was given to rule out the possibility of epidural vein and/or intrathecal placement.

All patients received a standardized general anesthetic consisting of 3 mg *d*-tubocrarine, 3-5 mg·kg^{-1} thiopental, 1.5 mg·kg^{-1} succinylcholine, 0.01-0.02 mg·kg^{-1} midazolam, and 3-10 μg·kg^{-1} fentanyl. Maintenance consisted of isoflurane (0.5-1.5% end tidal concentration), nitrous-oxide 60% and oxygen. Cis-atracurium, (0.3-0.5 mg·kg^{-1}), was used for neuromuscular relaxation. At the end of the procedure, neuromuscular blockade was reversed in all patients with 35-70 μg·kg^{-1} neostigmine and 5-10 μg·kg^{-1} glycopyrrolate. Intraoperatively, patients in both groups received up to 10 ml bupivacaine 0.5% in titrated doses to maintain analgesia, hemodynamic stability and surgical anesthesia.

The epidural infusions (Baxter AP II® pumps, Deerfield, IL. 60015) were started in the post anesthesia care unit (PACU) and titrated to keep pain Visual Analogue Scores (VAS) ≤ 25 (0 = no pain, 100 = worst possible pain) at rest. Patients with severe pain were given additional 5 ml boluses of epidural bupivacaine to keep pain VAS ≤ 25. Epidural narcotics were not bolused at any time for pain relief. Patients not responding to supplemental epidural local anesthetics were excluded from the study and given intravenous patient controlled analgesia (PCA) morphine. The following data were collected in the immediate postoperative period and every morning for the next three

TABLE I Demographic data, total bupivacaine and opioids, anti–nausea medications and the number of hospitalization days

	BM (*n* = 27)	*BF* (*n* = 33)	*P*
Age (yr)	57.6 ± 12.3	58.8 ± 14.4	0.733
Height (cm)	161.7 ± 4.7	160.7 ± 5.9	0.478
Weight (kg)	69.9 ± 19.0	73.3 ± 20.6	0.513
Total opioids used (mg)	22.4 ± 11.9	1.9 ± 1.1	–
Total bupivacaine used (mg)	468.7 ± 145.8	406.1 ± 135.9	0.335
Ondansetron injections	0.89 ± 1.05	0.81 ± 0.9	0.781
Prochlorperazine tablets	0.92 ±1.1	0.6 ±1.1	0.263
Hospitalization (days)	5.7 ± 2.4	4.5 ± 1.2	0.017

Legend: BM – bupivacaine morphine; BF – bupivacaine fentanyl. Total bupivacaine includes the amount administered as infusion. *P* values are not given for the total opioids used because the comparisons are not appropriate.

TABLE II Type of cancer and surgical operation

	BM (*n* = 27)	*BF* (*n* = 33)	*P*
Cancer Type (N)			
Uterine/Ovarian/Cervical	15	23	0.389
Other Pelvic	12	10	0.389
Operation Type			
TAH–BSO–Nodes	10	13	0.936
TAH–BSO	8	8	0.860
Radical Hysterectomy	5	3	0.492
Other pelvic	4	7	0.763

Legend: TAH–BSO–Nodes – Total abdominal hysterectomy and pelvic lymph node dissection. Other pelvic procedures include exploratory laparotomy with tumor debulking and second–look laparotomies for recurrent pelvic cancer. For other abbreviations see legend for Table I.

TABLE III Post Anesthesia Care Unit (PACU) data

	BM (n = 27)	*BF (n = 33)*	*P*
Pain VAS (range)	(0–70)	(0–100)	–
Pruritus VAS – median (range)	0 (0–15)	0 (0–70)	0.325
Bowel Function Variables			
Nausea VAS – median (range)	0 (0–90)	0 (0–50)	0.544
Emesis (%)	1 (3.7)	2 (6.0)	0.858
Nasogastric tube present (%)	12 (44.4)	13 (39.4)	0.895
Absence of bowel sounds (%)	27 (100)	29 (87.9)	0.176
Absence of flatus (%)	27 (100)	33 (100)	–
Absence of bowel movement (%)	27 (100)	33 (100)	–
Oral intake (%)	0 (0)	0 (0)	–

Legend: BM – bupivacaine morphine; BF – bupivacaine fentanyl. The median for pain VAS scores are given in Figures 1 and 2.

TABLE IV Data from Postoperative day 1

	BM (n = 27)	*BF (n = 33)*	*P*
Pain VAS at rest (range)	(0–75)	(0–100)	–
Pain VAS with movement (range)	(0–100)	(0–100)	–
Pruritus VAS – median (range)	0 (0–100)	0 (0–80)	0.879
Bowel Function Measured Variables			
Nausea VAS – median (range)	0 (0–90)	0 (0–70)	0.242
Emesis (%)	5 (18.5)	0 (0)	0.038
Nasogastric tube present (%)	12 (44.4)	13 (39.4)	0.975
Absence of bowel sounds (%)	18 (66.7)	14 (42.4)	0.134
Absence of flatus (%)	27 (100)	32 (97.0)	0.563
Absence of bowel movement (%)	27 (100)	33 (100)	–
Oral intake (%)	3 (11.1)	13 (39.4)	0.025

Legend: BM – bupivacaine morphine; BF – bupivacaine fentanyl. The median for pain VAS scores are given in Figures 1 and 2.

consecutive postoperative days (POD); 1) VAS scores for pain at rest and during movement, 2) VAS scores for nausea and pruritus, 3) presence of emesis, 4) return of bowel function as indicated by the presence of bowel sounds upon auscultation, the passage of flatus or stools, the continued need for a nasogastric tube and the ability to tolerate medications or clear fluids by mouth and 5) duration of hospitalization in days.

The Acute Pain Service of our department provided 24 hr postoperative pain management and the epidural infusions were adjusted to maintain pain VAS $\leq$ 25. As part of the SCP protocol all analgesic regimens were discontinued as soon as the patients were able to tolerate oral medication at which time they were given oral Percocet® tablets (5 mg oxycodone+325 mg acetaminophen) as needed for pain. Non steroidal anti-inflammatory drugs (NSAIDs) were not part of the SCP protocol and were not given. In accordance with the SCP protocol, patients with emesis or nausea were treated with prochlorperazine and/or ondansetron. On POD 1, the SCP protocol indicates assessing bowel sounds and if present, clamping the nasogastric tube for six hours. If no nausea or vomiting was evident, the nasogastric tube was removed. The following SCP criteria were used by the surgical service for discharge from the hospital: 1) ability to ambulate independently, 2) ability to tolerate a light oral diet, 3) afebrile (< 38°C), 4) incision site is clean, dry and intact, and 5) return of bowel function as indicated by first passage of flatus or stools. The discharge date was noted from the hospital records.

Statistical sample size calculation:

We used Thoren's[2] data to estimate the sample size. In his study, bowel function returned at 22 ± 16 hr in the epidural bupivacaine group and at 56 ± 22 hr in the epidural morphine group. We estimated that 25 patients were needed per group to detect a difference of 18 hr in the time of first flatus at an α of 0.05 and a power of 0.8. Results were expressed as mean ± 1 standard deviation (SD) or median. All interval data were compared using t test.[5] Frequency data were compared using contingency table analysis.[5] All VAS scores were compared using Mann- Whitney U-test.[5] A $P \leq 0.05$ was considered statistically significant.

Results

Sixty women (27-BM and 33-BF) completed the study. A sample size of 33 per group was chosen to allow for patients not completing the study. Six patients in the BM group did not complete the study (three bowel resections, one early epidural catheter dislodgement and two patients with inadequate analgesia despite repeated epidural injections).

No differences were noted with respect to age, height and weight between the two groups. (Table I). The total amounts of epidural opioids and bupivacaine used as well as the number of ondansetron injections and prochlorperazine tables given for nausea treatment did not differ between the two groups (Table I). The mean duration of a hospital stay was longer by one day in the BM group than in the BF group (Table I).

The specific types of cancer (uterine, ovarian, cervical or other) were similar between both groups (Table II) and so were the types of surgical procedures (Table II). All operations were laparotomies. All surgical approaches were done via a lower longitudinal midline incision, except for radical hysterectomies which were done via a low transverse abdominal incision. In our institution, the average duration of a total abdominal hysterectomy (TAH) is 2.0 ± 0.6 hr. The average duration of a TAH and bilateral salpingo-oophorecto-

TABLE V Postoperative day 2 collected data

	BM (n = 27)	*BF (n = 33)*	*P*
Pain VAS at rest (range)	0–60	0–75	–
Pain VAS with movement (range)	0–80	0–80	–
Pruritus VAS – median (range)	0 (0–80)	0 (0–80)	0.732
Bowel Function Measured Variables			
Nausea VAS – median (range)	0 (0–90)	0 (0–75)	0.615
Emesis (%)	4 (14.8)	1 (3.1)	0.256
Nasogastric tube present (%)	7 (25.9)	4 (12.1)	0.325
Absence of bowel sounds (%)	7 (25.9)	4 (12.1)	0.325
Absence of flatus (%)	26 (96.3)	32 (96.9)	0.549
Absence of bowel movement (%)	27 (100)	33 (100)	–
Oral intake (%)	14 (51.9)	21(63.6)	0.420

Legend: BM – bupivacaine morphine; BF – bupivacaine fentanyl. The median for pain VAS scores are given in Figures 1 and 2.

TABLE VI Postoperative day 3 collected data

	BM (n = 27)	*BF (n = 33)*	*P*
Pain VAS at rest (range)	0–100	0–100	–
Pain VAS with movement (range)	0–100	0–100	–
Pruritus VAS – median (range)	0 (0–50)	0 (0–70)	0.481
Bowel Function Measured Variables			
Nausea VAS – median (range)	0 (0–70)	0 (0–75)	0.584
Emesis (%)	2 (7.4)	5 (15.2)	0.570
Nasogastric tube present (%)	2 (7.4)	0 (0)	0.398
Absence of bowel sounds (%)	0 (0)	3 (9.1)	0.299
Absence of flatus (%)	20 (74.1)	21 (63.6)	0.676
Absence of bowel movement (%)	23 (85.2)	26 (78.8)	0.919
Oral intake (%)	18 (66.7)	21 (63.6)	0.848

Legend: BM – bupivacaine morphine; BF – bupivacaine fentanyl. The median for pain VAS scores are given in Figures 1 and 2.

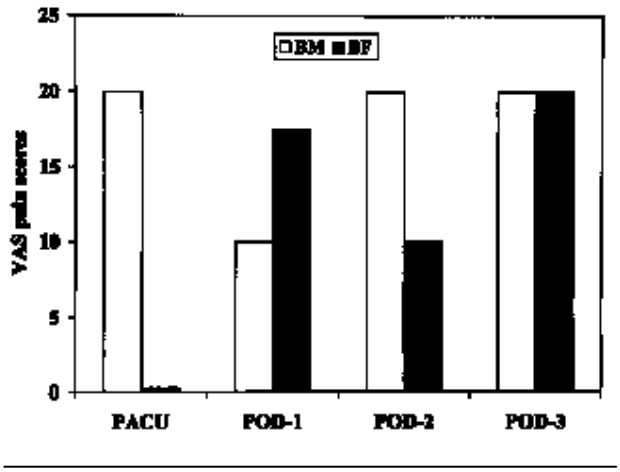

FIGURE 1 Median VAS pain scores at rest with bupivacaine–morphine (BM) and bupivacaine–fentanyl (BF) infusions. No differences were noted in any measurements in the post anesthesia care unit (PACU) or any postoperative day (POD). For pain scores ranges, please see Tables III–VI.

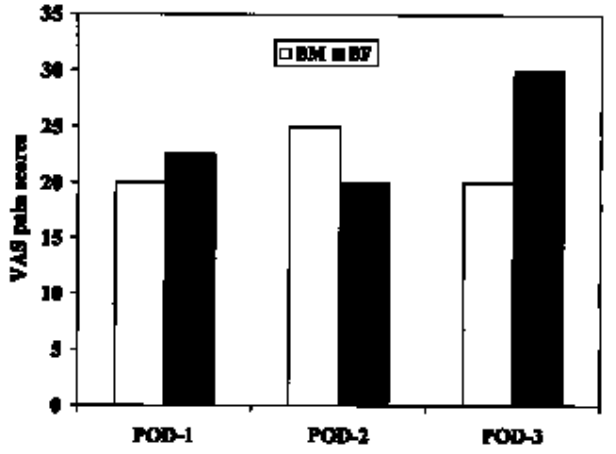

FIGURE 2 Median VAS pain scores during movement with bupivacaine–morphine (BM) and bupivacaine–fentanyl (BF) infusions. VAS pain scores during movement were not obtained in the PACU because the patients were awakening from anesthesia. No differences were noted in any of the measurements on any postoperative day (POD). For pain scores ranges, please see Tables IV–VI.

my with lymph node sampling (TAH-BSO-Nodes) is 2.5 ± 0.8 hr and a radical hysterectomy is 3.5 ± 1.0 hr.

Data collected in the post anaesthesia care unit (PACU) are presented in Table III. No differences were noted with respect to pruritus or pain scores or indices of bowel function: nausea, emesis, the presence of a nasogastric tube, the return of bowel sounds, or the passage of flatus or stools.

On POD 1, nausea VAS and pruritus VAS scores were similar in both groups (Table IV). Median pain VAS scores both at rest and during movement did not differ between the two groups (Figures 1, 2). Bowel function recovery as indicated by the presence of a nasogastric tube, absence of bowel sounds, absence of flatus and bowel movement were also similar between groups (Table IV). However, other indices of bowel dysfunction such as emesis and inability to tolerate clear oral fluids were more frequent in the BM group (Table IV). Pain scores (Figures 1,2) as well as nausea, pruritus scores and the indices of bowel function recovery were similar between groups on POD 2 and POD 3 (Tables V, VI).

Discussion

Our data show that both epidural BM and BF provided equally effective postoperative analgesia at rest and during movement. Epidural BF is associated with less emesis and an increased ability to tolerate oral fluids than BM on POD 1. Of the two infusions, epidural BF is associated with a shorter hospital stay.

Several studies have confirmed our results showing similar analgesia with continuous epidural BM and BF.[6–8] Other than nausea as a marker for return of bowel function, no study has compared the effects of continuous epidural fentanyl and morphine on postoperative gastrointestinal recovery. Fischer *et al.* concluded that continuous epidural BF resulted in less nausea than BM but this study lasted only 24 hr.[8]

Thoracic epidural analgesia is believed to produce superior postoperative analgesia with earlier return of bowel function after major abdominal surgery than lumbar epidural analgesia.[9] The evidence for this comes from a retrospective study which noted that the return of bowel function following proctocolectomy occurred earlier with thoracic epidural analgesia when compared to lumbar epidural analgesia although the days of hospitalization were similar in both groups (9.2 ± 4.1 thoracic *vs* 10.5 ± 6.3 lumbar).[10] In our study, the duration of hospitalization is nearly half that noted in the above study. Problems associated with thoracic epidural blocks include the increased risk of sympathectomy producing orthostatic hypotension.[1,7] In our institution we have successfully used a lumbar approach for the past ten years for postoperative analgesia following major pelvic surgery thus minimizing the potentially deleterious effects on blood pressure.

Major intra-abdominal surgery is associated with some degree of paralytic ileus. When bowel function returns in the postoperative period, the small intestine recovers first (< 24 hr), followed by the stomach (24 to 48 hr) and finally, the large intestine which can take up to 72 hr for complete recovery.[11] The exact mechanism of the perpetuation of postoperative ileus is not clear but is believed to be due to a variety of factors including pain, neural reflexes, hormones, medications, peritoneal irritation, length of surgery and other local factors.[9,11] Although return of bowel sounds heralds the restoration of peristalsis, the passage of flatus confirms the presence of a propagated peristaltic wave. The onset of gastrointestinal peristalsis decreases abdominal distension due to fluid and gas, thus diminishing the need for a nasogastric tube. In addition, it reduces the sensation of nausea and enables the patient to tolerate an oral intake. In our study, BM caused more emesis with less oral intake only on POD 1 and the BM group was also associated with a one day longer hospitalization period. Other markers for bowel dysfunction showed no differences and over the course of hospitalization, emesis and oral intake became insignificant.

Opioid effects on the gastrointestinal system are mediated by spinal μ, δ, and κ opioid receptors.[12] Opioids decrease gastrointestinal motility by inhibiting propulsive migrating myoelectric complexes (MMC) as well as enhancing the amplitude of nonpropulsive MMC.[13–15] In addition, opioids exert a direct effect on the submucosal plexus by inhibiting the stimulatory effects of acetylcholine, prostaglandin E_2, and vasoactive intestinal peptide.[13]

Hydrophilic opioids such as morphine diffuse into the CSF readily and migrate cephalad to the medulla oblongata and cerebral ventricles. Emesis is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema.[13,15] Injection of opioids into the cerebral ventricles or the spinal cord area can inhibit gastrointestinal propulsive activity as long as extrinsic innervation to the bowel is intact.[13,15] Epidural morphine, because of its hydrophilic nature and spread to the CTZ is most likely the reason why more emesis was noted on POD 1. The reason why more emesis was not noted on POD 2 and 3 is that the epidural infusions were titrated to decrease or eliminate side effects of the infusion and additionally, patients were treated for emesis and nausea.

Following epidural administration, morphine results in considerable plasma and cerebrospinal fluid levels.[15] Morphine undergoes conjugation to morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). The compound M6G is 62 times more potent in inhibiting gastrointestinal motility than the parent compound.[14] Compound M6G is most likely a contributing reason why fewer patients were able to tolerate clear oral fluids on POD 1.

Epidural BM is associated with a longer hospital stay than is BF. The SCP protocol used in our institution allows us to control for many factors that determine the duration of a hospital stay. The reason for the prolonged hospitalization of epidural BM is not clear. We do not know if the slower return of bowel function on POD 1 contributed to the prolonged hospitalization.

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