Pre- and intraoperative epidural ropivacaine have no early preemptive analgesic effect in major gynecological tumour surgery

[L'administration préopératoire et peropératoire de ropivacaïne n'a pas d'effet analgésique préventif précoce pour l'opération majeure d'une tumeur gynécologique]

Marc A. Burmeister MD, André Gottschalk MD, Marc Freitag MD, Ernst P. Horn MD, Corinna Böhme, Cornelia Becker MD, Thomas G. Standl MD

Purpose: Thoracic epidural analgesia (TEA) is an established technique for postoperative pain relief after major abdominal surgery. However it is still under discussion whether pre-incisional TEA can reduce postoperative pain perception or postoperative analgesic consumption.

Methods: The present prospective, randomized, double-blind study was performed to investigate the effects of intra- and postoperative TEA *vs* only postoperative TEA using ropivacaine 0.375% in 30 women scheduled for major abdominal tumour surgery. Prior to induction of general anesthesia patients received an epidural bolus of 10 mL saline in Group I (GI) and 10 mL ropivacaine 0.375% in Group II (GII) followed by an infusion of 6 mL·hr^{-1} of the respective solution during surgery. Postoperatively all patients received an epidural infusion of 6 mL·hr^{-1} ropivacaine 0.375% during 24 hr followed by patient controlled epidural analgesia for the next 72 hr. Operative data, dynamic pain scores, consumption of local anesthetics and standardized supplemental analgesics were analyzed.

Results: No difference was seen between groups with respect to the amount of required postoperative local anesthetics and supplemental analgesics, pain scores and side effects during the first 96 hr following surgery except a reduction of intraoperative sufentanil consumption (GI: 143.2 ± 52.6 *vs* GII: 73.3 ± 32.6 μg, $P < 0.001$).

Conclusion: Intraoperative TEA with ropivacaine 0.375% did not significantly reduce the amount of analgesics required after major abdominal gynecological tumour surgery.

Objectif : *L'analgésie péridurale thoracique (APT) est une technique reconnue pour l'analgésie suivant une opération abdominale majeure. Mais on se demande encore si l'administration d'APT avant l'incision peut réduire la perception de la douleur ou la consommation d'analgésique postopératoires.*

Méthode : *La présente étude prospective, randomisée et en double aveugle a été réalisée pour rechercher les effets de l'APT peropératoire et postopératoire vs l'APT postopératoire seulement à base de ropivacaïne à 0,375 % chez 30 patientes subissant une opération majeure pour tumeur abdominale. Avant l'induction de l'anesthésie générale, les patientes ont reçu un bolus péridural de 10 mL d'une solution saline dans le Groupe I (GI) et 10 mL de ropivacaïne à 0,375 % dans le Groupe II (GII), suivi d'une perfusion de 6 mL·h^{-1} de la solution respective pendant l'opération. Après l'opération, toutes les patientes ont reçu une perfusion péridurale de 6 mL·h^{-1} de ropivacaïne à 0,375 % pendant 24 h, suivie d'une analgésie péridurale autocontrôlée pour les 72 h suivantes. Les données opératoires, les scores de douleur dynamiques, la consommation d'anesthésiques locaux et d'analgésiques supplémentaires normalisés ont été analysés.*

Résultats : *Il n'y avait aucune différence intergroupe quant à la quantité d'anesthésiques locaux et supplémentaires postopératoires, aux scores de douleur et aux effets secondaires pendant les 96 premières heures postopératoires, sauf une réduction de la consommation de sufentanil peropératoire (GI : 143,2 ± 52,6 vs GII : 73,3 ± 32,6 μg, $P < 0,001$).*

Conclusion : *L'APT peropératoire utilisant de la ropivacaïne à 0,375 % ne réduit pas significativement la quantité d'analgésique nécessaire après une opération majeure pour tumeur gynécologique abdominale.*

From the Department of Anesthesia, University Hospital Hamburg-Eppendorf, Hamburg, Germany.

Address correspondence to: Dr. Marc A. Burmeister, Department of Anesthesia, University Hospital Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany. Phone: +49-40-42803-2415/4525; Fax: +49-40-42803-4963; E-mail: burmeister@uke.uni-hamburg.de

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THORACIC epidural analgesia (TEA) is an effective technique to reduce postoperative pain in patients undergoing major abdominal surgery.[1–4] However, the results of the intraoperative use of TEA in combination with general anesthesia are still controversial with respect to a reduction of postoperative pain perception or postoperative analgesic consumption.[5–10] This can be explained in part by the variety of types and sites of surgery,[11] or by the presence or absence of pain before surgery.[12] In a recently published review Moiniche *et al.* pointed out that preemptive continuous epidural treatment extending into the postoperative period might have an improved capacity to reduce nociceptive input and thereby central neuroplasticity caused not only by incision and ongoing surgery but also by postsurgical inflammation.[13] For this reason standardized studies are necessary for different types of surgery, patients and treatment. The present prospective, randomized, double-blind study was performed in 30 women scheduled for extended elective ovarian tumour surgery to test the hypothesis that additional pre- and intraoperative epidural infusion of ropivacaine 0.375% can reduce the postoperative pain perception and requirement of analgesics in comparison with only systemic intraoperative analgesia.

Methods

After approval of the local Ethics Committee and informed written consent, 30 women (ASA I–III, 37–82 yr) undergoing major abdominal gynecological tumour surgery because of ovarian cancer were included in this prospective, randomized and double-blinded study. Patients had no history of neurologic disorders, major vertebral abnormalities or coagulation disorders. Patients with any kind of analgesic medication or preexisting pain with a visual analogue scale (VAS) score of more than 10 mm using a VAS (0 mm = no pain, 100 mm = unbearable pain) were excluded.

On the day of surgery patients were premedicated orally with 7.5 mg midazolam (Hofmann-La Roche, Grenzach-Wyhlen, Germany) 60 min before arriving in the anesthesia room where they were monitored by an electrocardiogram (ECG), noninvasive measurement of blood pressure and pulse oximetry. Following the *iv* infusion of 500 mL of Ringer's solution a thoracic epidural catheter was placed before general anesthesia was induced.

All patients were awake during insertion and testing of the epidural catheter. With the patient in the sitting position, a deep skin infiltration with 3–5 mL lidocaine 1% (AstraZeneca, Wedel, Germany) was performed for local anesthesia before the 18-G Tuohy needle (B. Braun, Melsungen, Germany) was inserted at the T8 ± 1 level. After the loss of resistance had been obtained, a 22-G end-hole catheter (B. Braun) was inserted 4 cm into the epidural space. A test dose of 3 mL plain mepivacaine 2% (AstraZeneca) was injected after negative aspiration. All catheters were tunnelled subcutaneously 5 cm to the right or left side and secured with a single stitch at the skin outlet. Five minutes later, patients were randomly allocated to receive 10 mL NaCl 0.9% in Group I (GI) or 10 mL ropivacaine 0.375% (AstraZeneca) in Group II (GII) using a computer-generated random list (MS Excel, Microsoft Inc., Redmond, WA, USA) via the epidural catheter. Patients and investigators were blinded to study groups. Twenty minutes after the epidural injection, general anesthesia was induced with 0.4 $\mu g \cdot kg^{-1}$ sufentanil and 0.25 $g \cdot kg^{-1}$ etomidate lipuro *iv* (B. Braun). To facilitate orotracheal intubation, cisatracurium 0.15 $mg \cdot kg^{-1}$ (GlaxoSmithKline, Bad Oldesloe, Germany) was given. A central venous catheter was inserted via the external or internal jugular vein. Anesthesia was maintained with isoflurane (0.5 vol%, end-tidal) in nitrous oxide and 30% oxygen. Patients received repetitive boli of sufentanil for analgesia depending on predefined clinical criteria (tachycardia > 90 $beats \cdot min^{-1}$ and mean arterial pressure (MAP) > 90 mmHg if hypovolemia was excluded by central venous pressure > 5 mmHg measurement). Until incision no additional sufentanil was given in both groups.

The first injection was immediately followed by a continuous epidural infusion of 6 $mL \cdot hr^{-1}$ of the respective study medication until the end of surgery. After completion of surgery (end of skin closure) patients of both groups received a continuous epidural infusion of 6 $mL \cdot hr^{-1}$ ropivacaine 0.375% and were transferred to the intensive care unit (ICU), where mechanical ventilation was discontinued after a stabilization period until patients reached predefined extubation criteria (body temperature 36.5–38.0°C, MAP > 60 mmHg without vasoconstrictors, PaO_2 > 80 mmHg with 30% oxygen, no surgical bleeding). Twenty-four hours after the start of the epidural infusion, pain management was changed from continuous to patient controlled epidural analgesia (PCEA) with ropivacaine 0.375% in both groups using the Graseby 9300 infusion pump (SIMS, Graseby Ltd, Watford, UK). The basal infusion rate was 4 $mL \cdot hr^{-1}$ with a bolus of 2 mL and a lock-out interval of 15 min. During the entire postoperative observation period patients were allowed to receive piritramide *iv* as a supplemental analgesic (15 mg piritramide are equivalent to 10 mg morphine), if pain at rest was > 40 mm on the VAS and the allowed bolus of 2 mL ropivacaine 0.375% was not able to control pain within 15 min.

TABLE Demographic and perioperative variables

	Group I *n = 15*	*Group II* *n = 15*	*P value*
Age (yr)	58.3 ± 10.5	57.9 ± 10.1	0.99
Height (cm)	165.9 ± 4.9	167.7 ± 5.9	0.99
Weight (kg)	65.5 ± 14.7	70.1 ± 16.1	0.87
ASA Class I/II/III	0/13/2	0/14/1	0.64
Duration of surgery (hr)	5.9 ± 1.6	6.4 ± 1.9	0.74
iv sufentanil (μg)	143.2 ± 52.6	73.3 ± 32.6	0.01*
Resection of bowel or small intestine (%)	66	79	0.68
Intraoperative blood loss (L)	2.4 ± 1.6	3.2 ± 1.8	0.21
Intraoperative fluid sustitution (L)			
Ringer's lactate	3.8 ± 1.4	4.3 ± 1.7	0.38
Colloids	1.8 ± 0.5	2.1 ± 0.5	0.13
RBCs (L)	1.4 ± 1.1	1.3 ± 1.5	0.71
FFPs (L)	2.9 ± 3.1	3.0 ± 2.5	0.94
Intraoperative vasoconstrictors			
Theodrenaline + caphedrine (number of patients)	13	15	0.48
Theodrenaline + caphedrine (cumulative dose mL) (1 mL contains 100 mg theodrenaline and 5 mg caphedrine)	1.3 ± 1.1	1.9 ± 1.6	0.24
Norepinephrine infusion (number of patients)	5	5	1.00
Norepinephrine infusion (cumulative dose μg)	126 ± 276	348 ± 672	0.25
Postoperative mechanical ventilation (min)	215 ± 180	195 ± 200	0.48
ICU stay (days)	1.4 ± 1.1	1.5 ± 1.1	0.95
Hospital stay (days)	14.5 ± 6.1	14.1 ± 3.1	0.83

All data mean ± SD unless indicated otherwise. RBC = red blood cells; FFP = fresh frozen plasma; ICU = intensive care unit.

The quality of analgesia was assessed by an anesthesiologist blinded to the group assignments at rest and during mobilization (sitting on the bedside) 24, 48, 72 and 96 hr after the start of the epidural infusion using a VAS. Intensity of motor block (Bromage scale 0–3), upper and lower level of analgesia (pinprick test), side effects (nausea, vomiting, pruritus, shivering, bladder dysfunction), cumulative amount of infused study solutions, demanded and received PCEA-boli, and cumulative supplemental piritramide requirements were recorded. Patients were asked and examined for complications or side effects associated with epidural anesthesia such as persisting motor block, bladder dysfunction, postdural puncture headache and radicular irritation up to the seventh postoperative day. Intraoperative blood and fluid losses and requirements were recorded.

Sample size calculation and statistical analysis

Sample size was calculated on the basis of retrospective data from our institution in the same surgical population. A power analysis was performed by using the cumulative consumption of administered study solution over four days as the primary outcome variable. We set 6 $mL \cdot hr^{-1}$ as the mean dose of epidurally required analgesic. This translates into a cumulative dose of 576 mL over the whole study period of 96 hr. For calculation of the sample size, we decided the smallest difference to be clinically significant was 25% (144 mL) of the cumulative amount of epidural analgesics over four days. The anticipated pooled standard deviation was set at 100 mL of the cumulative dose. We would permit a type I error of $\alpha = 0.05$, and with the alternate hypothesis, the null hypothesis would be retained with a type II error of $ß = 0.05$. This analysis reaches a power of 0.95 and indicated that a sample size of at least 14 patients per group was necessary.

Computerized statistical analysis was performed using SPSS 9.0 (SPSS Inc., Chicago, IL, USA) and Instat 2.1 (Graphpad Inc., San Diego, CA, USA). Data are given as mean ± SD unless otherwise indicated. Demographic and perioperative data including hemodynamics and volume of epidural infusion were tested using unpaired Student's t test. Statistical methods included Mann Whitney U test for VAS values, upper and lower level of epidural block and piritramide requirements. Chi square testing was used for side effects and intensity of motor block. $P < 0.05$ was considered significant.

Results

Demographic characteristics and intraoperative hemodynamics

Patients of both groups had no relevant pre-existing pain (GI: 1.7 ± 0.5 *vs* GII: 1.9 ± 0.3). All patients underwent standardized surgery including longitudinal abdominal incision from the pubic symphysis to the lower end of the sternum, radical resection of the ovaries, uterus, inguinal and obturator lymph nodes. The greater omentum, peritoneal metastases or parts of the bowel or small intestine were resected in 66% and 79% of patients in GII and I respectively.

As shown in the Table patients did not differ in demographic characteristics such as age, height, weight and ASA status. Duration of surgery, intraoperative blood loss, amount of transfused red blood cells and fresh frozen plasma, duration of stay in the ICU and total in-hospital stay was similar in both groups. The cumulative intraoperative dose of sufentanil was significantly higher in GI when compared with GII. No difference was observed in duration of postoperative mechanical ventilation. Details of the perioperative data are shown in the Table. Heart rate decreased after induction of anesthesia in both groups and was lower in GII at the end of surgery only (Figure 1a). The mean arterial blood pressure decreased in both groups after induction of general anesthesia and was significantly lower in GII *vs* GI at the time of surgical incision but comparable during the rest of surgery (Figure 1b).

Postoperative analgesia

The VAS values for postoperative pain are presented in Figure 2ab. There was no significant difference between the two groups at rest or during mobilization. The cumulative volume of the epidurally required ropivacaine was nearly identical in both groups and below the maximal possible volume (Figure 3). The cumulative dose of piritramide is also shown in Figure 3. Although there seems to be a trend towards a higher consumption in GII, the difference was not significant ($P = 0.24$ at the end of the observation period). Approximately half of the patients in each group demanded supplemental piritramide. Upper and lower levels of sensory block did not differ between groups during the entire observation period (range of upper/lower levels at 24 hr, GI: T4–8/L1–L3; GII: T5–7/T12–L2; at 48 hr, GI: T6–9/T12–L2; GII: T5–9/T11–L1; at 72 hr, G1: T6–9/T12–L1; GII: T6–9/T11–L2; at 96 hr, GI: T6–9/T12–L2; GII: T7–9/T11–L1).

Side effects

Relevant motor block (Bromage scale > 1, unable to rise knees against gravity) was observed in one patient of both groups. In GII one patient showed motor dysfunction (Bromage Grade 2) 48 hr after the start of epidural infusion which was not detectable thereafter. The patient in GI showed a paresis of the quadriceps muscle thought to be a direct irritation of the femoral nerve caused by surgical resection of the iliac lymph nodes. No complications associated with epidural anesthesia, such as PDPH

Figure 1a

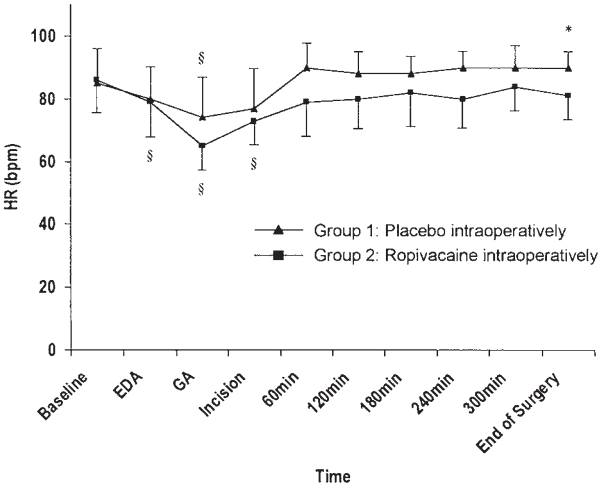

Figure 1b

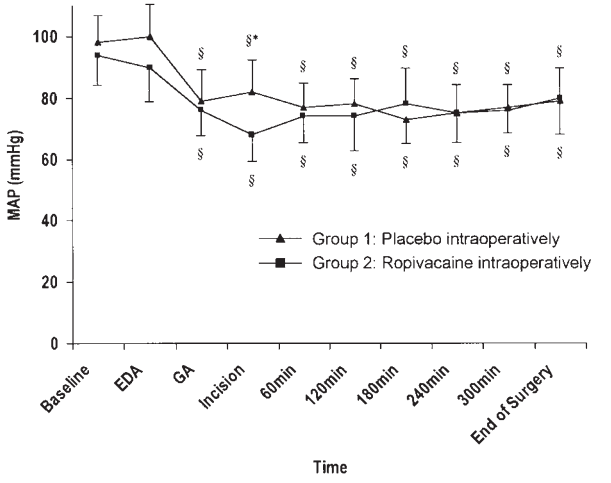

FIGURE 1 a) Intraoperative heart rate (HR); and b) mean arterial pressure (MAP) before insertion of the epidural catheter (baseline), after the first epidural injection (EDA), after induction of general anesthesia (GA), following surgical incision (incision), and after 60, 120, 180, 240, 300 min and at the end of surgery (mean ± SD). *$P < 0.05$ *vs* Group II, §$P < 0.05$ *vs* baseline.

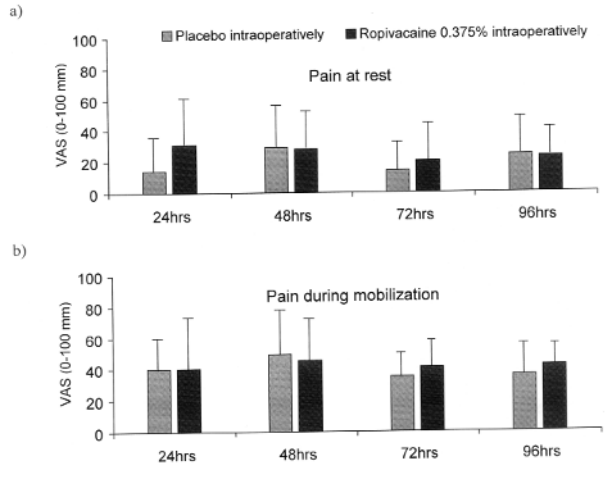

FIGURE 2 Visual analogue scale (VAS) values for pain assessed by patients at rest and during mobilization from 24 to 96 hr after surgery (mean ± SD).

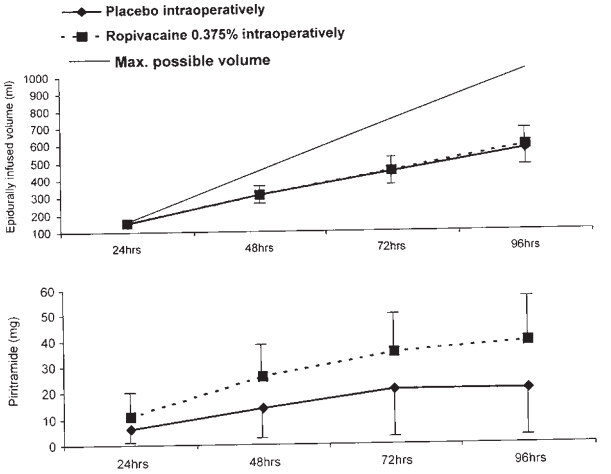

FIGURE 3 Cumulative consumption of epidural ropivacaine and supplemental *iv* piritramide from 24 to 96 hr after surgery (mean ± SD).

or radicular irritation were seen up to the seventh postoperative day in any of the patients.

Discussion

In the present study pre-surgical and intraoperative epidural administration of ropivacaine 0.375% reduced the intraoperative requirements of *iv* sufentanil but was not able to reduce pain or analgesic requirements in the early postoperative period after major abdominal surgery in gynecological patients. Epidural analgesia with ropivacaine 0.375% provided adequate postoperative analgesia during 96 hr, only low doses of supplemental *iv* analgesics being required in both study groups. The effect of intraoperative administration of ropivacaine on the development of chronic pain was not assessed in our study.

As already mentioned, the preemptive analgesic effect appears to be dependent on the type of surgery. The preemptive analgesic effect of epidurally administered local anesthetics in abdominal gynecological surgery remains unclear. Our results are in accordance with the findings of Aida *et al.*, who also found no preemptive effect of pre-surgical epidural analgesia in abdominal surgery using morphine. One main reason for the ineffectiveness of epidural analgesia in visceroperitoneal surgery could be the heterosegmental innervation of the operated area, e.g., sensory innervation by the phrenic nerve, since epidural analgesia is only able to block the segmental innervation by spinal nerves. This problem seems to occur especially in upper abdominal surgery while in lower abdominal surgery the afferent parasympathetic innervation comes from the sacral spinal nerves which can be blocked via the spinal route. This might explain the preemptive analgesic effect described for radical prostatectomy.[6,14]

In contrast to the above-mentioned single drug applications, Rockemann *et al.* were able to reduce postoperative analgesic consumption in their study using a multimodal pre-surgical analgesic approach for major abdominal surgery.[15] Nevertheless, the use of nonsteroidal anti-inflammatory drugs should be evaluated critically, in the presence of potential major bleeding.

Another reason for the ineffectiveness of preemptive analgesia could be pre-existing pain. As described by Aida *et al.* central sensitization seems to be already established by pre-surgical acute or chronic pain and preserved until the termination of surgery.[12] Therefore we included only patients with a preoperative VAS score for pain at rest of 10 mm or less.

Epidural analgesia resulted in a significantly reduced intraoperative opioid requirement in patients of GII in comparison to GI. The higher dosage of intraoperative opioids in GI probably compensated the lack of epidural blockade, in order to provide analgesia comparable to the combination of both techniques in GII. The higher cumulative sufentanil doses in GI did not lead to prolonged mechanical ventilation under the conditions of this study which included transfer of the propofol sedated patients to the ICU and stabilization of temperature and cardiocirculatory variables after the extended surgery.

In spite of contradictory results of studies concerning preemptive analgesia and the lack of effects in the meta-analysis by Moiniche, the concept of preemptive analgesia still remains a topic of intense discussions.[13,16,17] Further investigations with respect to mechanisms of development and treatment strategies are required.

In conclusion the pre- and intraoperative epidural administration of ropivacaine 0.375% showed no early preemptive analgesic effect in women undergoing extended abdominal tumour surgery.

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