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Continuous Elastomeric Pump-Based Ropivacaine Wound Instillation after Open Abdominal Aortic Surgery: How Reliable Is the Technique?

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ABSTRACT

Introduction: We aimed at quantifying the impact of continuous wound infusion with ropivacaine 0.33% on morphine administration and subjective pain relief in patients after open abdominal aortic repair in a double-blind, placebo-controlled study.

Methods: Before closing the abdominal wound, 2 multihole ON-Q® Soaker Catheters™ (I-Flow Corporation, Lake Forest, California, USA) were placed pre-peritoneally in opposite directions. Either ropivacaine 0.33% or saline 0.9% was delivered by an elastomeric pump at a rate of 2 mL/h for 72 hours in each of the catheters. Postoperative pain and morphine administration were assessed using the numerical rating scale (NRS) in 4-hour intervals. Total plasma concentrations of ropivacaine, unbound ropivacaine, and α1-acid glycoprotein (AAG) were measured daily. Mean arterial pressure, pulse rate, oxygen saturation, total amount of morphine administration, ventilation time, and length of stay in the intensive care unit (ICU) were recorded. At the end of the study period, the wound site and the condition of the catheters were assessed.

Results: The study was terminated prematurely due to a malfunction of the elastomeric balloon pump resulting in toxic serum levels of total ropivacaine in 2 patients (11.4 µmol/L and 10.0 µmol/L, respectively) on the second postoperative day. Six patients had been allocated to the ropivacaine group, and 9 patients had been allocated to the control group. Demographic and surgical data were similar in both groups. During the first 3 postoperative days, no difference between the ropivacaine and the control group was found in NRS (P = .15, P = .46, and P = .88, respectively) and morphine administration (P = .48). Concentrations of unbound serum ropivacaine (0.11 ± 0.08 µmol/L) were below toxic level in all patients.

Conclusion: Continuous wound infusion of ropivacaine 0.33% 2 mL/h using an elastomeric system was not reliable and did not improve postoperative pain control in patients after open abdominal aortic surgery.

INTRODUCTION

Appropriate and sufficient postoperative pain treatment reduces postoperative morbidity and costs and improves patient outcome [Kehlet 2001; Kehlet 2002]. Although regional techniques, eg, epidural anesthesia or continuous peripheral nerve blockade, can provide high-quality postoperative analgesia [Block 2003; Richman 2006], these procedures may be restricted by various factors such as costs, failure rate, and the experience of the staff. Local anesthetic wound infiltration is a simple technique and widely used as part of a multimodal approach to postoperative pain management. In contrast to a single bolus administration of local anesthetic, prolonged administration through a multi-holed catheter may improve the efficacy of local wound infiltration. The catheters are positioned by the surgeon before skin closure. This technique has been successfully performed after major gynecological [Gómez Rios 2009], urological [Forastiere 2008], thoracic [Wheatley 2005; Salvemini 2008], reconstructive [Dateline 2009], abdominal colorectal [Fredman 2001; Beaussier 2007; Polglase 2007], or cardiac [White 2003; Magnano 2005] surgery. In most cases, continuous wound infiltrations led to pain relief and to a reduction in systemic opioid use and opioid-related side effects. The benefits and safety of this approach were recently confirmed by a systematic review of randomized controlled trials [Liu 2006]. The analgesic effect of continuous wound infiltration may vary according to the type of surgical procedure [Fredman 2001; Magnano 2005], the placement strategies [Levack 1986], and the type, volume, and concentration of the local anesthetic used. Recently, the ON-Q® PainBuster® Post-Op Pain Relief System (I-Flow Corporation, Lake Forest, California, USA) has been introduced. The system consists of an elastomeric pump connected through a flow-limiting valve to a small flexible multi-hole catheter that acts as a soaker hose and allows continuous infiltration of local anesthetics into the tissue at a constant rate. The aim of this randomized, double-blind, placebo-controlled study was to quantify the impact of

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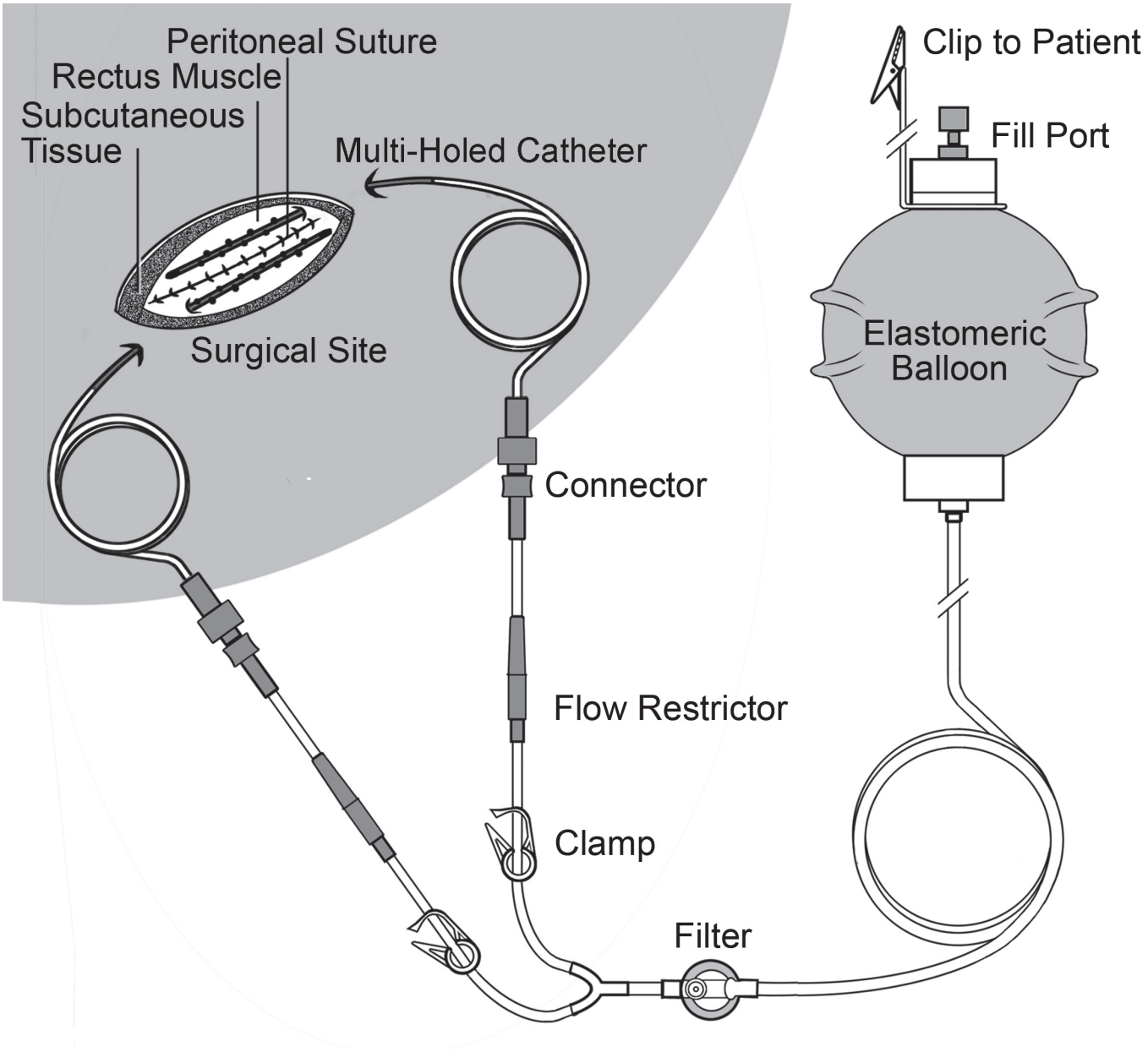

Figure 1. The elastomeric balloon pump system. Two multi-holed catheters connected via a Y piece were fed by the same elastomere pump system.

a continuous pre-peritoneal wound infiltration with ropivacaine 0.33% on morphine administration and subjective pain relief in patients after open abdominal aortic repair. Blood concentrations of total and unbound plasma ropivacaine were measured to assess the safety of the technique.

MATERIALS AND METHODS

The study was approved by the Local Research Ethics Committee (EK number StV 6-2007). Based on primary endpoint, ie, the cumulative morphine consumption at the third postoperative day, we calculated a sample size of 40 patients in order to have 90% power to detect a 20% difference in morphine administration between the groups, using a paired t test with a .05 2-sided significance level.

Written informed consent was obtained from all patients before study enrollment. Patients included were scheduled for open abdominal aortic surgery and were ≥18 years. Exclusion criteria were non–German-speaking patients, patients participating in other studies, and patients with a history of adverse reactions to local anesthetics, chronic hepatic disease, body mass index (BMI) ≥ 35 kg/m^2, chronic pain disease, chronic opioid treatment, latex allergy, neurologic diseases, and neuropsychiatric disorders. Patients were specifically instructed

Table 1. Demographic and Procedural Data*

	Ropivacaine	Control	*P*
Sex (f/m)	1/5	1/8	
Age, y	69 ± 10	66 ± 11	.50
Weight, kg	79.0 ± 9.37	6. ± 10.3	.79
Length, cm	172 ± 6	172 ± 9	.83
Body mass index, kg/m^2	26.6 ± 2.7	26.1 ± 5.83	
Surgery time, min	219 ± 86	190 ± 90	.37
Fentanyl, mg	0.9 ± 0.3	0.9 ± 0.25	.96
Remifentanil, mg	2.8 ± 1.3	3.1 ± 1.5	.78
Ventilation time, min	195 ± 308	156 ± 247	.23
ICU time, h	21.8 ± 3.8	18.9 ± 6.7	.18
RASS POD 1	–0.3 ± 0.8	–0.2 ± 0.4	.74
RASS POD 2	–0.7 ± 1.6	0.1 ± 0.4	.20
RASS POD 3	–0.6 ± 1.3	0.1 ± 0.4	.17

*Data are expressed as mean ± standard deviation. ICU indicates intensive care unit; RASS POD x, Richmond agitation and sedation scale at postoperative day x.

in the use of the numeric rating scale (NRS) to rate their incision pain on a scale ranging from 0 (no pain) to 10 (maximum pain imaginable) on the eve of the surgery.

The patients were randomly allocated with computer-generated randomization to receive a continuous wound infusion of either 0.33% ropivacaine (Naropin, AstraZeneca GmbH, Wedel, Germany) or 0.9% saline. Upon arrival in the preparation room, an independent anesthetist prepared a pump filled either with 0.33% ropivacaine (group R) or 0.9% saline (control group, group C) according to the randomization. Only the pharmacist of the hospital was aware of the type of solution to be administered; physicians, attending staff in charge of the patient, and the patients were fully blinded to the patient's group assignment.

Patients were premedicated with oral flunitrazepam (1.0-2.0 mg) on the evening before surgery and with oral midazolam (7.5-15 mg) 45 minutes before transfer to the operating room. Standard monitoring included a 2-channel electrocardiograph (ECG) (leads II and V5; Hellige SMU 612 monitor, Marquette Hellige Medical Systems, Freiburg i.Br, Germany), pulse oximetry using a finger clip (Nellcor™ Durasensor® DS-100A; Covidien-Nellcor, Boulder, Colorado, USA), and continuous arterial blood pressure monitoring (Hellige SMU 612 monitor, Marquette Hellige Medical Systems) via a fluid-filled catheter system (Baxter Healthcare Corporation Cardiovascular Group, Irvine, CA, USA) connected to the non-dominant radial artery.

Induction of anesthesia was performed using target-controlled infusion technique with propofol (target plasma concentration: 2.5-4.0 µg/mL), supplemented by bolus injections of fentanyl (1-3 µg/kg) and atracurium (0.6 mg/kg). During the procedure, anesthesia was maintained with propofol (target plasma concentration: 1.5-2.0 µg/mL) and remifentanil (0.1-0.3 µg/kg per minute). All patients were orally intubated and mechanically ventilated (Siemens Servo 900 C; Erlangen, Germany). A 4-lumen central venous catheter (Arrow International, Reading, Pennsylvania, USA) was inserted into the right jugular vein. At the end of surgery, after closure of the parietal peritoneal membrane, the surgeon inserted 2 20-gauge multi-holed Soaker Catheters (ON-Q PainBuster) 6.5 cm until 12.5-cm long, approximately 3 cm from the lower and 3 cm from the upper end of the midline incision through an introducer needle in the opposite direction. Both catheters were positioned 1 cm next to the midline of the incision between the previously closed parietal peritoneal membrane and the lower side of the transverse fascia, along the entire length of the wound (Figure 1). After closing the fascia and the skin, 10 mL 0.9% saline was injected through both catheters to prevent occlusion. The prefilled elastomeric pump (ON-Q PainBuster) was connected to the 2 multi-holed ON-Q Soaker Catheters via a Y piece. The pump was set to deliver a constant rate of 2 mL/h per catheter during the next 72 hours (a total of 316.8 mg/24 h). The catheters were covered with a transparent dressing. Depending on the surgical progress, patients recovered from anesthesia in the theater or in the intensive care unit (ICU). If necessary, residual neuromuscular block was neutralized by atropine and neostigmine.

Additional postoperative pain management was strictly identical for all patients. Basis medication included paracetamol (0.5-1 g, 4 times a day) and metamizole (0.5-1 g, 4 times a day) administered intravenously on a fixed schedule. For break-through pain, patients received weight-adjusted bolus injections of morphine sulfate if NRS was ≥ 3. Pain was assessed by the investigators every 20 minutes during the first hour in the ICU, and 4-hourly until the end of the investigation (postoperative day 3 [POD 3]). Special attention was given to clinical signs and symptoms of local anesthetic toxicity such as light-headedness, tinnitus, and seizures, noting that those signs could be tempered by paracetamol or morphine.

Venous blood samples were taken daily during the investigation period (POD 1 to POD 3). Total plasma concentrations of ropivacaine (total ropivacaine) and unbound plasma concentrations of ropivacaine (free ropivacaine) were determined. Levels of α1-acid glycoprotein (AAG) were also measured, because it has the potential advantage of buffering the free ropivacaine, providing a protective mechanism against toxic reactions. Total ropivacaine concentration was determined by liquid chromatography with mass spectrometry using electrospray ionization. Free ropivacaine was determined by the same method following ultrafiltration of the sample. Concentrations of AAG were measured by nephelometry.

Partial arterial oxygen tension (PaO_2), arterial oxygen saturation (SaO_2), pulse rate, mean arterial pressure (MAP), and the Richmond agitation sedation scale (RASS) were recorded every 4 hours until discharge from the ICU. As soon as the patient reached the ward pulse rate, MAP, oxygen saturation measured by pulse oximetry (SpO_2), and RASS were recorded every 4 hours until the end of the study period. Ventilation time after arrival in the ICU,

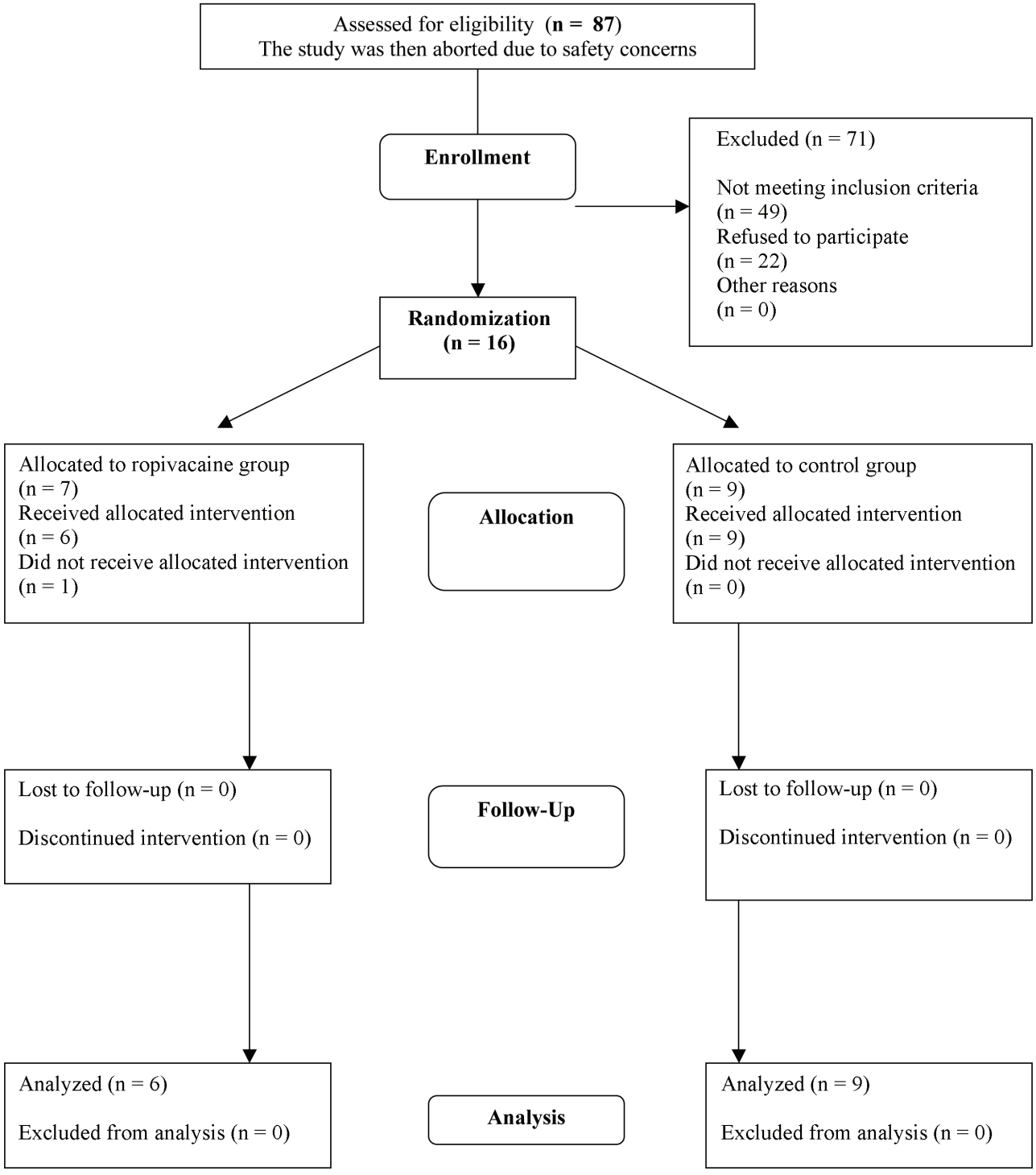

Figure 2. Consort flow chart of the randomization process. The study was aborted after the assessment of 87 patients.

signs of local wound infection, complications, and length of stay in the ICU were also documented. Seventy-two hours (POD 3) after the end of the surgery, the catheters were removed and the functionality was tested by flushing them with saline.

The statistical analyses were performed using SPSS® version 16 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are summarized as mean ± standard deviation. Analysis of variance (ANOVA) for repeated measures was used to analyze all parameters with post hoc comparison and Bonferroni correction.

Table 2. Serum Concentration of Total Ropivacaine, Unbound Ropivacaine, and α1-Acid Glucoprotein*

	POD 1	POD 2	POD 3
Total ropivacaine, μmol/L	1.24 ± 1.22	5.44 ± 3.50	4.35 ± 2.79
Free ropivacaine, μmol/L	0.05 ± 0.04	0.16 ± 0.10	0.11 ± 0.06
α1-acid glucoprotein, μmol/L	0.77 ± 0.13	1.3 ± 0.33	1.62 ± 0.43

*Data are expressed as mean ± standard deviation. POD indicates postoperative day.

RESULTS

We decided to stop the study prematurely because of serious safety concerns regarding malfunction of the elastomere balloons. In 2 patients the elastomeric pump was found empty on POD 2, which implies that the infusion rate must have been significantly higher than the protocol infusion rate of 2 mL/min. Accordingly, the total ropivacaine plasma concentration was 11.4 μmol/L and 10.0 μmol/L, respectively, in these patients. At the time of the termination of the study, 16 patients had been enrolled (Figure 2): 6 patients in the ropivacaine group and 9 patients in the control group. One patient in the ropivacaine group had to be excluded from the analysis because of an accidental removal of 1 of the multi-hole catheters at arrival in the ICU.

Demographic data, surgery time, intraoperative opioid administration, length of ICU stay, and RASS postoperatively were similar in both groups (Table 1).

During the first postoperative day (POD 1), NRS was lower in group R (2.4 ± 1.8) compared to group C (4.0 ± 1.9), but this difference did not reach statistical significance (P = .14). Also, no significant difference was found on POD 2 (R: 4.6 ± 2.9; C: 3.7 ± 1.7; P = .46) and POD 3 (R: 3.0 ± 2.4; C: 2.8 ± 2.3; P = .88) (Figure 3A). Cumulative morphine administration was similar in both groups (R: 81.1 ± 46.8 mg; C: 99.7 ± 49.0 mg: P = .48) (Figure 3B).

None of the patients showed clinical symptoms of toxicity. Serum concentrations of free ropivacaine (0.11 ± 0.08 μmol/L) were within the normal range (toxic level: > 0.55 ± 0.29 μmol/L) (Table 2, Figure 4). Postoperatively, AAG concentration was continuously increasing during the whole investigative period. Total ropivacaine showed a significant variation with concentrations well above the normal range, with the highest value measured at POD 2. The peak of plasma concentrations of total ropivacaine and free ropivacaine was reached on POD 2 (Figure 4).

PaO_2 (P = .89), ventilation time (P = .23), and length of stay (P = .18) in the ICU (Table 1) did not differ significantly between groups. Similarly, RASS, pulse rate, and MAP were found in both groups on all 3 PODs. At POD 2 the SpO_2 was significantly higher in group R (P = .02), but the corresponding FiO_2 administered was also significantly higher (P = .04) (data not shown). Inspection of the removed catheters at the end of the investigation period revealed that in 33% of the multi-hole catheters, ≥ 50% of the orifices were closed. No wound infection was observed in either groups.

DISCUSSION

The main findings of this study were (1) the unpredicted high total plasma concentrations of ropivacaine caused by an inconsistent flow in the multi-hole catheters and (2) a missing improvement in pain relief.

Local anesthetic wound infiltration is not a new technique [Vintar 2002], and it is based on the considerable impact of local nociceptive afferents on overall pain. Open abdominal aortic surgery induces severe and prolonged postoperative pain, at rest and in particular during mobilization. Systemic opiates are not always efficacious to completely treat postoperative pain without considerable side effects such as drowsiness, postoperative nausea and vomiting, and disturbance of the bowel function. A few studies in patients with infra-renal aortic repair have shown a marked benefit of epidural local anesthetics in pain control and reduction of morbidity [Flores 2002; Muehling 2009]. A number of medical conditions and comorbidities, however, prohibit the use of epidural analgesia. Furthermore, in approximately 30% of all cases, efficient pain relief is not achieved because of technical failure [Ready 1999]. Continuous local anesthetic wound infusion thus may be an alternative option, and its use has been described as mostly beneficial in several studies [Fredman 2001; White 2003; Beaussier 2007; Polglase 2007].

The ON-Q PainBuster System was Not Reliable in Administration of Continuous Wound Instillation of Local Anesthetics

With the administration of ropivacaine 0.33% 2 mL/h through each multi-hole catheter, the patients received a total of about 317 mg ropivacaine per day, which is well below the suggested maximal daily dose of 700 mg. This dose is usually considered safe for a continuous infusion over several days. There is, however, a recent report that recommends a cautious use of continuous infusion of local anesthetics in patients undergoing cardiovascular surgery because of the risk of toxic levels of ropivacaine [Maurer 2008]. In that study ropivacaine was delivered via an extrapleural catheter. After 48 hours, 2 of the patients reached toxic levels of both total and free plasma ropivacaine. As a possible cause, the authors proposed that a combination of factors such as patient comorbidities and surgeries associated with major fluid shifts may have caused these findings. In addition to these variables, there were several strong hints in our study that the infusion rates of the elastomeric balloon system were not stable. The fact that 2 of the elastomeric balloons were emptied out already on POD 2 suggested a much higher rate of infusion than a total of 4 mL/h for both catheters, which led to abortion of the study ahead of schedule to avoid any further risk of toxicity in the study patients. The 2 affected patients also showed by far the highest concentrations of total plasma ropivacaine. Toward the end of the infusion, the rate was probably rather low, which was illustrated by a decreasing concentration of the unbound serum ropivacaine on POD 3. It is very unusual that plasma concentrations of local anesthetics are decreasing when administered continuously at the same rate. The documented constant increase in AAG would at most explain in

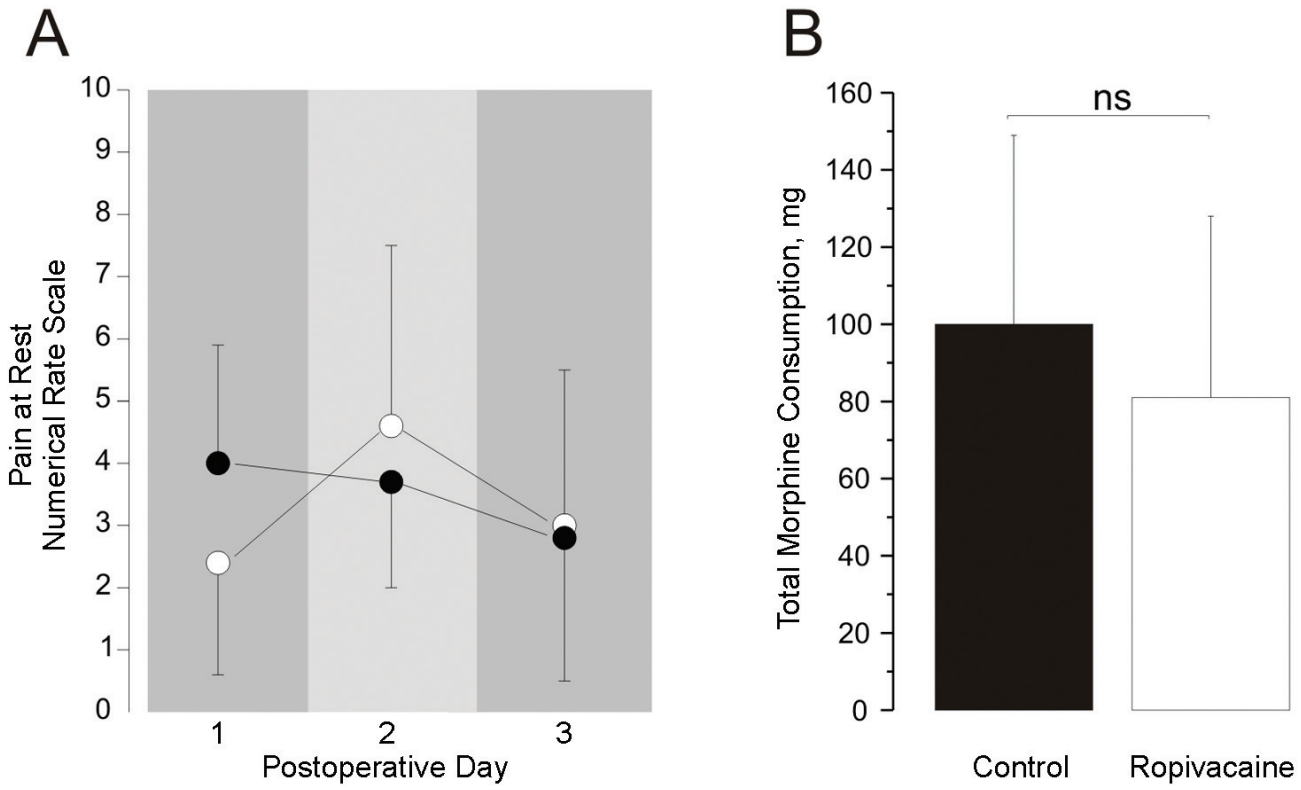

Figure 3. A, Average pain scores with standard deviation over the investigation period; zero indicates no pain, and 10 indicates the worst pain imaginable. B, Cumulative amount of morphine at the end of the investigation period. Values are presented as mean ± standard deviation.

part a lack of accumulation of the free ropivacaine; however, no investigation thus far has showed that an increase in AAG causes a decrease in concentration of unbound local anesthetics after any kind of surgery. In combination with the fact that total ropivacaine plasma concentrations stared to decrease on POD 3, we assume that the infusion rates of all the elastomeric balloons in this study were variable and did not reflect at all the preset rate.

One cause may be a manufacturing error of the elastomeric balloon of the ON-Q PainBuster system, but the most likely explanation was an unreliable function of the flow-limiting valve. Additionally, the flow controlled by the flow-limiting valve is dependant on the body temperature, as stated by the manufacturer. Low body temperature leads to a reduction in flow, and high body temperature to an increased flow in the multi-hole catheters. Unfortunately, body surface temperature was not determined in this study, so no statement can be made about the possible influence of increased body surface temperature. Inspection of the catheters after removal showed an obstruction of a fraction of orifices in most of the catheters. It would seem possible that the onset of wound healing led to an early closure of individual orifices and therefore interfered with the flow rate. Otherwise, an inconstant flow rate might also have led to an obstruction of a number of orifices of the catheter. Previous investigations with similar pump systems confirm the variability of drug delivery by elastomeric balloons [Thiveaud 2005].

Continuous Wound Instillation of Ropivacaine Did Not Improve Pain Control

We are aware that we have to be very careful in drawing conclusions regarding the effect on pain relief between the 2 investigated groups because we aborted the study for safety concerns and did not reach the numbers of study patients to achieve the desired power. Other factors, however, may have contributed as well to the lack of difference and are discussed here.

In the current study, continuous infiltration of ropivacaine only into the pre-peritoneal layer was performed. This method has been successfully used in patients scheduled for colorectal surgery [Beaussier 2007] and is based on the knowledge that incision of the parietal peritoneum is especially likely to contribute to postoperative pain and may be involved in several perioperative complications, such as prolonged paralytic ileus [Beaussier 2007]. However, activation of the sensory nerves of the subcutaneous layer of the abdominal wall has limited impact on the overall pain after laparatomy [Fredman 2001; Baig 2006]. To our knowledge, continuous infiltration has never been used in open abdominal aortic repair. Only Pfeiffer and colleagues have investigated the impact of frequently repeated bolus wound instillations of a local anesthetic in patients undergoing aortic surgery [Pfeiffer 1991]. Seventy-two patients were randomized to receive either 40 mL bupivacaine 0.25% or 40 mL saline through 2 indwelling wound irrigation catheters every 4 hours.

The catheters were placed either subcutaneously or into the rectus layer. The authors reported that repeated bolus administration of local anesthetics neither improved pulmonary function nor reduced morphine requirements when compared to saline instillation. In contrast to the method they used, the current investigation was performed with continuous instillation of 2 mL/h ropivacaine 0.33% in each of the multi-hole catheters, and the pre-peritoneal space was instilled using the ON-Q PainBuster system as described by Beaussier and collegues [Beaussier 2007]. They reported significantly reduced morphine consumption, improved pain relief, and accelerated postoperative recovery by continuous instillation of ropivacaine 0.2% 10 mL/h in the pre-peritoneal layer of patients undergoing laparatomy for colorectal surgery.

In the current study we have shown that continuous infiltration of ropivacaine 0.33% into the pre-peritoneal layer using the ON-Q PainBuster system did not reduce pain sensation and opiate consumption. Unlike other studies, no initial bolus was given to avoid a possible initial overdose of ropivacaine. Neurologic signs of an overdose might have been missed in these patients, because the probability of postoperative cognitive dysfunction is considerable in the setting of cardiovascular surgery. The RASS, a reliable tool to detect these issues, was equal in both groups. It confirmed that our patients did not suffer from systemic toxicity.

There are several limitations of this study. The main limitation was the abortion of the study ahead of schedule to avoid any risk of toxicity in the study patients. Thus the power of the current analysis is limited. However, the reason for discontinuation of the study, a major and potentially dangerous malfunction of the elsastomeric balloon system, is worth being communicated, because the unpredictable flow of the elastomeric balloon system represents an incalculable risk of intoxication for the patients. Another limitation might be that no initial bolus was given before starting continuous infiltration, which might have resulted in an initially insufficient anesthetic drug concentration. Gomez and colleagues (Gómez Rios 2009), however, reported effective pain relief caused by only 2 mL/h bupivacaine 0.2% after abdominal hysterectomy. Last but not least, in open abdominal aortic surgery the prime anatomical location of pain generation is not entirely clear because there are 2 important layers that are injured: the abdominal wall and the retroperitoneal wall including the aortic wall. Possible deep somatic pain of the retroperitoneal space might have considerable impact in the overall pain sensation in these patients. If so, only a part of pain sensation would be treated with the continuous wound infusion of local anesthetic in the pre-peritoneal space.

We conclude, therefore, that clearly further investigations are necessary to clarify the optimal device, the volume, the concentration, and the localization of the continuous wound infusion of local anesthetics in this patient population.

Continuous pre-peritoneal infusion of ropivacaine 0.33% 4 mL/h using the ON-Q PainBuster system was not reliable in administration of the preset volume and did not improve postoperative pain control in patients after open abdominal aortic surgery.

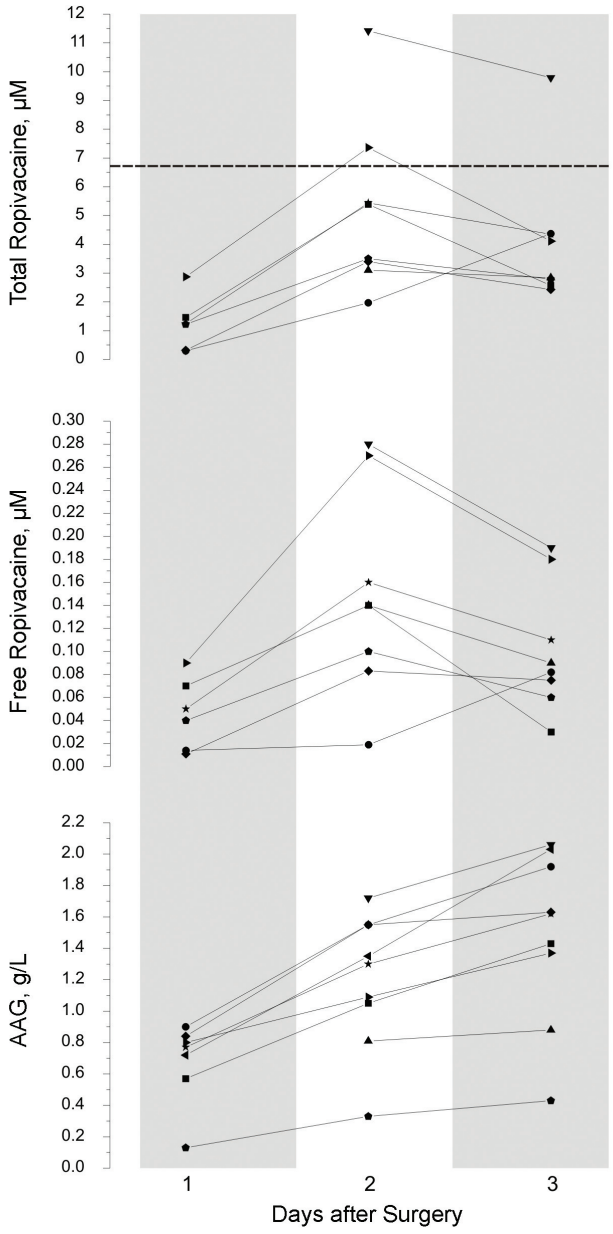

Figure 4. Plasma concentration of total ropivacaine, free ropivacaine, and α1-acid glycoprotein (AAG). Plasma concentrations were measured during a 72-hour wound infiltration of 2 × 2 mL/h ropivacaine 0.33%. Each line represents 1 patient. The thick dashed line marks the total ropivacaine limits considered non-toxic.

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