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Epidural Ropivacaine Concentrations for Intraoperative Analgesia During Major Upper Abdominal Surgery: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Study

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BACKGROUND: The postoperative beneficial effects of thoracic epidural analgesia (TEA) within various clinical pathways are well documented. However, intraoperative data are lacking on the effect of different epidurally administered concentrations of local anesthetics on inhaled anesthetic, fluid and vasopressor requirement, and hemodynamic changes. We performed this study among patients undergoing major upper abdominal surgery under combined TEA and general anesthesia.

METHODS: Forty-five patients undergoing major upper abdominal surgery were randomly assigned to one of three treatment groups receiving intraoperative TEA with either 10 mL of 0.5% (Group 1) or 0.2% (Group 2) ropivacaine (both with 0.5 μg/mL sufentanil supplement), or 10 mL saline (Group 3) every 60 min. Anesthesia was maintained with desflurane in nitrous oxide (60%) initiated at an age-adapted 1 minimum alveolar concentration (MAC) until incision. Desflurane administration was then titrated to maintain an anesthetic level between 50 and 55, as assessed by continuous Bispectral Index monitoring and the common clinical signs (PRST score). Lack of intraoperative analgesia, as defined by an increase in pulse rate, sweating, and tearing (PRST) score >2 or an increase of mean arterial blood pressure (MAP) >20% of baseline, was treated by readjusting the end-tidal concentration of desflurane toward 1 MAC, and above this level by additional rescue IV remifentanil infusion. Hypotension, as defined as a decrease in MAP >20% of baseline, was treated by reducing the end-tidal desflurane concentration to a Bispectral Index level of 50–55 and below that with crystalloid or norepinephrine infusion, depending on central venous pressure.

RESULTS: End-tidal desflurane concentration could be significantly reduced in Group 1 to 0.7 ± 0.1 MAC ($P < 0.001$) and to 0.8 ± 0.1 MAC ($P < 0.001$) in Group 2, but not in Group 3. Significant hypotension occurred within 20 min in all patients of Groups 1 and 2 (MAP from 80 ± 10 to 56 ± 5) (Group 1), 78 ± 18 to 58 ± 7 mm Hg (Group 2), $P < 0.01$, whereas MAP remained unchanged in Group 3 (74 ± 12 to 83 ± 15 mm Hg, $P = 0.42$). Heart rate did not change significantly over time within any of the groups. Furthermore, groups did not differ significantly regarding IV fluid and norepinephrine requirement. Patients in Group 3 received more remifentanil throughout the surgical procedure (7.2 ± 4.9 $mg \cdot kg^{-1} \cdot h^{-1}$) when compared with Group 2 (1.6 ± 2.2 $mg \cdot kg^{-1} \cdot h^{-1}$), $P < 0.01$. Remifentanil infusion among patients receiving ropivacaine 0.5% was not necessary at any time.

CONCLUSION: Epidural administration of 0.5% ropivacaine leads to a more pronounced sparing effect on desflurane concentration for an adequate anesthetic depth when compared with a 0.2% concentration of ropivacaine at comparable levels of vasopressor support and IV fluid requirement.

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The combination of thoracic epidural analgesia (TEA) and general anesthesia (GA) has become a widespread anesthetic technique for the perioperative treatment of patients undergoing major abdominal surgery. The benefits of postoperative TEA compared with IV patient-controlled opioid analgesia were pointed out in a recent meta-analysis.[1] The neuraxial application of local anesthetics and opioids provides superior pain relief, reduced hormonal and metabolic stress, enhanced normalization of gastrointestinal

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Table 1. Patients' Characteristics: Data are Presented as Mean Values ± SD and Number of Patients

	Group 1 ropivacaine 0.5% (n = 15)	Group 2 ropivacaine 0.2% (n = 13)	Group 3 controls (n = 15)
No. of patients	15	13	15
Age (yr)	59 ± 12	61 ± 11	59 ± 14
Height (cm)	173 ± 8	172 ± 10	170 ± 8
Weight (kg)	83 ± 15	76 ± 15	71 ± 16
Gender (m/f)	11/4	8/5	9/6
Concomitant medication			
β-blockers (n)	2	3	3
ACE-inhibitors (n)	5	6	5
Ca^{2+}-channel blockers (n)	3	1	1
Duration of surgery (min)	340.1 ± 103	325 ± 91	308 ± 139
Type of surgery			
PPPD (n)	6	7	8
Hepatectomy (n)	7	4	4
Gastrectomy (n)	2	2	3

Patients' characteristics, type, and duration of surgery and concomitant medication: Data are presented as means ± SD or number of patients. There were no significant differences among groups.
PPPD = pancreaticoduodenectomy; ACE = angiotensin converting enzyme.

function, and thus a shortened postoperative recovery time, facilitating mobilization and physiotherapy. TEA is currently thought to mitigate this effect by blocking nociceptive afferent nerves and thoracolumbar sympathetic efferent routes.[2,3]

Among the long-acting local anesthetics, the *S*-enantiomer, ropivacaine, is gaining increasing preference for continuous epidural analgesia. Ropivacaine has lower central nervous system and cardiac toxicity, and a less frequent incidence of unintended motor block (differential block) during mobilization than bupivacaine.[4] The effects of different ropivacaine dosage regimes, with and without additives such as opioids or clonidine, have been reported for postoperative pain relief[5–12]; however, there are no data concerning the intraoperative effects of different concentrations of local anesthetics on the requirement of volatile anesthetics or on hemodynamics.

We hypothesized that higher concentrations of epidurally administered ropivacaine would lead to a more pronounced reduction of desflurane requirement (primary outcome) and to a more distinct impairment of hemodynamics, thus requiring more vasopressor and IV fluid support (secondary outcome).

METHODS

Patients

After institutional approval (Ethics committee of the Faculty of Medicine, University of Technology Dresden EK-DD 187102003) and written informed consent, 45 patients, aged 51–66 yr, ASA physical state II and III, who were scheduled for major upper abdominal surgery (Table 1) with TEA and GA, were enrolled in the study.

Patients were randomly assigned to one of three treatment groups, intraoperatively receiving either epidural ropivacaine 0.5% + 0.5 μg/mL sufentanil (Group 1), or ropivacaine 0.2% + 0.5μg/mL sufentanil (Group 2), or saline (control Group 3). The solutions were prepared by a nurse according to a computer-derived block randomization list. Syringes were delivered to the operating room (OR) merely labeled with "TEAMAC-Study" and the consecutive patient number. The attending anesthesiologist was blinded to patient randomization. Exclusion criteria were patient's refusal of epidural analgesia, obesity (body mass index >30), a history of drug and alcohol abuse, preoperative analgesic therapy, cerebrovascular and central nervous system diseases, preexisting bleeding or coagulation disorders, concomitant antiplatelet therapy, known allergic diathesis to drugs and pregnancy.

Preoperative Arrangements/Monitoring

Patients were NPO 2 h before induction and received 7.5 mg midazolam (Dormicum®, Roche Deutschland Holding GmbH, Grenznach-Wyhlen, Germany) orally 45 min before arrival in the OR. Concomitant medication including antihypertensives, such as β-blockers, angiotensin converting enzyme inhibitors, and Ca channel blockers were continued as indicated by the standard operating procedures of the department. A 5-lead electrocardiogram including measurement of segmental ST depression (II, aVF, V5), and pulse oximetry were recorded. Arterial blood pressure was monitored continuously via the left radial artery (IntelliVue®, MP70, Philips, Böblingen, Germany). A central venous line was placed in the innominate (brachiocephalic) vein for continuous monitoring of central venous pressure. Anesthetic depth was assessed by the Bispectral Index® (BIS) monitor (BIS sensor, Aspect Medical Systems, software version 3.2, Natick, MA) and the PRST score (based on heart rate, arterial blood pressure, diaphoresis, and lacrimation, Appendix).

Thoracic Epidural Analgesia

In the sitting position before induction, an epidural catheter was inserted at a target midthoracic level through an 18-gauge Tuohy needle with the bevel

cephalad (Perisafe® Plus, BD, Bidford-on-Avon, UK) using the loss-of-resistance to saline technique. The catheter was advanced 3–4 cm into the epidural space. After a negative aspiration test to detect IV misplacement, a test dose of 4 mL of lidocaine 2% without epinephrine was injected to uncover unintended subarachnoid catheter placement. For intraoperative analgesia, 10 mL of the study solution was injected epidurally every 60 min. The dose was not adjusted in case of hypotension.

General Anesthesia

GA was induced with 1.5 mg/kg propofol (Propofol® 1%, Fresenius-Kabi, Bad Homburg, Germany) and 0.5 μg/kg sufentanil (Sufentanil®, Janssen-Cilag, Neuss, Germany). Tracheal intubation was facilitated by 0.5 mg/kg rocuronium (Esmeron®, Organon, Oberschleißheim, Germany). GA was maintained with desflurane (Suprane®, Baxter, Unterschleißheim, Germany) in O_2/N_2O (35%/60%). Patients' lungs were mechanically ventilated with a minute volume adequate to maintain end-tidal Pco_2 of 36–40 mm Hg at a fresh gas flow of 1 L/min. (Primus®, Dräger, Lübeck, Germany).

Study Protocol

The first dose of the epidural study solution was injected after induction of GA and at least 20 min before surgery to achieve adequate distribution within the epidural space. Until the start of surgery, end-tidal desflurane concentration was corrected for age and N_2O_ adapted at 1 minimum alveolar concentration (MAC), according to the Iso-MAC charts for desflurane by Nickalls and Mapleson.[13] The end-tidal desflurane concentration, the respective BIS value and PRST score were documented as baseline values.

IV fluids and vasopressors were administered as follows: decrease in mean arterial blood pressure (MAP) >20% to baseline before induction was treated by decreasing the end-tidal concentration of desflurane up to a BIS level of 50–55 and increasing the IV preload with crystalloids up to a maximum central venous pressure of 10 mm Hg. If hypotension persisted, norepinephrine (Arterenol®, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) was continuously infused to restore MAP to at least 80% of baseline.

The end-tidal desflurane concentration was continuously adjusted during surgery to maintain BIS within the intended range of 50–55, allowing a stabilization phase of 5 min after each readjustment. An increase in BIS >55, even without changes in the PRST score, was treated by increasing the end-tidal concentration of desflurane until a maximum end-tidal desflurane concentration of an age-adapted 1 MAC. Above this level, increases in the PRST score >2 points or MAP ≥20% of baseline values were treated by additional IV remifentanil (Ultiva®, GlaxoSmithKline, Munich, Germany) as rescue analgesia, starting with 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until the PRST score and MAP decreased to baseline values. If BIS values decreased below 50–55, remifentanil was tapered to zero.

Estimated blood loss was replaced with hydroxyethel starch 130 (Voluven®, Fresenius-Kabi, Bad Homburg, Germany) until a hematocrit of 25% was achieved before red packed cells were transfused.

Adverse hemodynamic responses were defined as hypertension (increase in systolic arterial blood pressure >20% baseline), hypotension (decrease in systolic blood pressure >20% baseline), tachycardia (increase in heart rate >30% baseline), and bradycardia (decrease in heart rate >30% baseline). Bradycardia below 45/min was treated by 0.01 mg/kg atropine.

Possible interactions of the BIS monitor with increased electromyographic activity were controlled throughout the study period by the continuous index of electromyographic activity on the BIS XP platform and a simultaneous control of recovery from neuromuscular blockade by electrical stimulation of the ulnar nerve at the wrist by the nerve stimulator (Innervator® NS 252, Fisher & Paykel, Healthcare, Auckland, New Zealand) using the train-of-four stimuli (2 Hz for 2 s).

Postoperative Follow-Up

After skin closure, the volatile anesthetic was discontinued and after tracheal extubation in the OR, patients of all groups immediately received 0.2% ropivacaine and 0.5 μg/mL sufentanil via an infusion pump for patient-controlled epidural analgesia at a rate of 10 mL/h, with the possibility of a bolus of 5 mL, followed by a lockout period of 20 min. To detect intraoperative awareness or recall, patients were interviewed using the Brice questionnaire immediately after surgery, and 2 days later when they were discharge.[14] Using cold sensations the extent of the epidural blockade was tested immediately after arrival in the postanesthesia care unit or the intensive care unit and at least three times a day by the attending acute pain service anesthesiologist. After surgery, all patients received patient controlled epidural analgesia via a Baxter I Pump®, (Baxter, Deerfield, IL), with a continuous infusion of ropivacaine 0.2% at 5 mL/h and 0.5 μg/mL sufentanil supplement, with the possibility of a 5 mL bolus administration at a lockout time of 20 min.

Statistics

Statistical analysis was performed using the Statistical Program for Social Sciences for Windows (SPSS®, release 12.0, Chicago, IL). Doses of ropivacaine and sufentanil, as well as the required number of patients, were calculated on the basis of a previous investigation: A power analysis based on a pilot study (patients received 10 mL 0.3% ropivacaine with 10 μg sufentanil as supplement every 60 min) suggested that a sample size of 15 patients should be adequate to detect a 50% reduction of the end-tidal concentration (25% of MAC

Table 2. Intraoperative Requirement of Fluids, Norepinephrine, and Total Dose of Ropivacaine

	Group 1 ropivacaine 0.5% ($n = 15$)	Group 2 ropivacaine 0.2% ($n = 13$)	Group 3 controls ($n = 15$)
Intraoperative			
Crystalloids ($mL \cdot kg^{-1} \cdot h^{-1}$)	6.8 ± 2.5	7.5 ± 3.4	8.0 ± 3.9
Colloids ($mL \cdot kg^{-1} \cdot h^{-1}$)	1.2 ± 1.1	2.2 ± 1.0	1.7 ± 1.7
NE ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.05 ± 0.06	.05 ± 0.04	0.02 ± 0.04
Total ropivacaine* (mg)	242 ± 102	91 ± 27	

Intraoperative requirement of fluids, norepinephrine, and total dose of ropivacaine. Data are presented as means ± SD or number of patients.

NE = norepinephrine.

*$P < 0.001$.

values) of desflurane with a power of 0.8 ($\alpha = 0.05$) at equal BIS level, with a sufficient distribution among the dermatomes of the upper abdomen.[15]

Categorical values are presented as percentage and were analyzed with the Fisher's exact χ^2-test and the Wilcoxon's ranked sum test. Continuous values are presented as means ± SD using analysis of variance. Bonferroni adjustment was applied if multiple comparisons of data were made. A general linear model was used for comparison of continuous data among groups over time.

RESULTS

Epidural catheter placement at a target level of Th 7-8, and subsequent combined anesthesia was performed in all patients. There were no statistical differences regarding patient characteristics, comorbidity, type and duration of surgery, and concomitant medication (Table 1). Forty-five patients consented to the investigation and were included in the study. Because of protocol violations in terms of remifentanil administration at desflurane levels <1 MAC, two patients from Group 2 were withdrawn from the database. All other 43 screened patients were included in the analysis.

The end-tidal desflurane concentration was reduced in Group 1 from 1 MAC (2.6 vol%) to 0.7 ± 0.1 MAC (1.3 ± 0.2 vol%, $P < 0.001$ vs control group and $P = 0.001$ vs. Group 2) and to 0.8 ± 0.1 MAC in Group 2 (1.8 ± 0.3 vol%), $P < 0.001$ vs control group in contrast to Group 3. However, in Group 2, intermittent administration of remifentanil (1.6 ± 2.2 mg/h) was necessary because of transient signs of inadequate analgesia. In Group 3, the end-tidal desflurane concentration could not be reduced. In all Group 3 patients, significantly more remifentanil was continuously administered throughout the surgical procedure (7.2 ± 4.9 mg/h) when compared with patients receiving 0.2% ropivacaine (1.6 ± 2.2 $mg \cdot kg^{-1} \cdot h^{-1}$), $P < 0.01$. Remifentanil infusion among patients receiving ropivacaine 0.5% was not necessary.

Desflurane administration was adjusted to the actual demand under continuous BIS and PRST score monitoring. Downward titration was more often required in the 0.5% ropivacaine group when compared with the 0.2% ropivacaine group (51 downward titrations in Group 0.5% vs 34 in Group 0.2% ropivacaine, $P < 0.01$). Hypotension occurred in all Group 1 and Group 2 patients after application of the epidural solution, which was initially treated by IV infusion of crystalloids and norepinephrine, $P < 0.05$. There were no differences within groups regarding requirement for crystalloids, colloids, and norepinephrine, to maintain MAP within ±20% of baseline values (Table 2). Because of the interventions per protocol (rescue analgesia, intravascular volume, and vasopressor support), hemodynamics were kept fairly constant during the observation period (Figs. 1 and 2).

According to the study protocol, the end-tidal concentration of desflurane was increased up to 1 MAC; above this level, remifentanil infusion was started.

There were no intra- and postoperative complications related to the anesthetic regimen (catheter misplacement, ischemic episodes, nerve injuries, or spinal hematoma). All epidural catheters were removed within 5 ± 2 days after surgery and all patients were

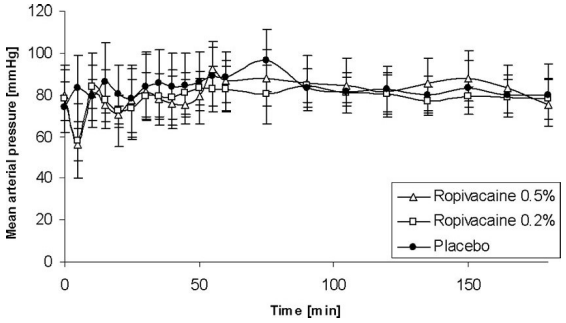

Figure 1. Course of mean arterial blood pressure (MAP) during surgery. Time point 0: First administration of study solution.

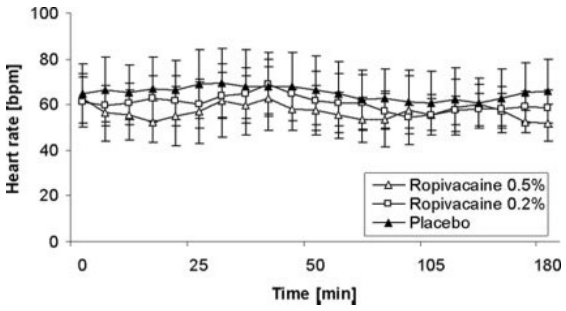

Figure 2. Intraoperative course of heart rate, time point 0: First epidural administration of study solution.

discharged home within 21 days after surgery. During the postoperative interviews, no patient reported intraoperative awareness or recall.

DISCUSSION

The effects of different concentrations and infusion rates of ropivacaine for postoperative pain relief have been broadly investigated.[5–12] In contrast, the effects of different, intraoperatively administered concentrations of ropivacaine on the required end-tidal concentration of volatile anesthetics ensuring an adequate anesthetic depth have not been reported, nor have their effects on hemodynamics and vasopressor and fluid demand.

Primarily, we investigated the primary effects of two different concentrations of epidurally administered ropivacaine on the desflurane concentration and secondarily their hemodynamic side effects, IV fluid supply and requirement of additional remifentanil infusion as rescue analgesia.

We did not observe a significant difference in the requirement for IV fluids or norepinephrine in our study, although the total ropivacaine dose was significantly higher in patients receiving 0.5% ropivacaine (Table 2).

One would expect that larger concentrations of ropivacaine would induce more frequent and more pronounced hypotension followed by higher vasopressor and volume demand. The explanation for the similar level of required fluids and vasopressor support that ropivacaine 0.2% did not provide adequate intraoperative analgesia in every patient, and thus, remifentanil was administered for rescue analgesia. The synergistic effects of epidurally administered ropivacaine 0.2% and sufentanil with remifentanil led to a more pronounced decrease in MAP compared with epidurally administered ropivacaine 0.5% with sufentanil alone.

However, our study was underpowered to evaluate the secondary outcomes of intraoperative fluid and vasopressor management. Because intraoperative fluid management during major upper abdominal may be influenced by many factors, such as intraoperative blood loss, duration of surgery, preoperative bowel preparation, and incision size, the intraoperative fluid requirement may not be attributed either to local anesthetic concentration, or the end-tidal desflurane concentration alone. To adequately address the possibility of a β error based on the current data, a case load of 182–956 patients in each group would have been required to gain statistically significant between-group differences in secondary outcomes.

The most difficult questions to address are how to distinguish between effective analgesia and adequate anesthesia and how to quantify intraoperative analgesia. We used the definition of intraoperative analgesia in the review by Guignard[14], where adequate analgesia is defined in terms of maintaining a stable hemodynamic status, both during and after a noxious stimulus. We therefore used the common clinical signs as, partially, included in the PRST score and added BIS monitoring, which has been quantified in several clinical trials.[16,17] However, local anesthetics and opioids administered epidurally not only block the nociceptive impulses from the surgical field at the spinal level but may also exert anesthetic properties due to rostral spread or systemic absorption of the drugs, thereby influencing hypnotic depth due to synergistic effects with volatile anesthetics.[18–21] Therefore, in our trial, we distinguished between inadequate analgesia (at a sufficient anesthetic depth of BIS $\leq$50) under 1 MAC desflurane and, simultaneously, changes of the clinical signs $\geq$20%, on the one hand, and inadequate hypnotic depth (BIS $>$55 with or without simultaneous changes of the clinical signs) on the other. The PRST score contains the most commonly used criteria for the assessment of hypnotic depth and effective analgesia in anesthetic practice. Although several concerns have been noted, the evaluation of clinical signs is still the most practical approach in clinical practice.[22]

Another methodological concern is the lack of a group receiving 0.5 μg/mL sufentanil alone. However, in this study, ropivacaine was the focus of our attention, although sufentanil was added only as a supplement to prolong the analgesic effects of ropivacaine. It seemed more clinically relevant to examine two ropivacaine concentrations against a placebo solution (10 mL 0.9% NaCl), which missing analgesic properties are clearly intraoperatively distinguishable.

In conclusion, ropivacaine 0.5% compared with a ropivacaine 0.2% concentration led to a greater inhaled anesthetic-sparing effect at the same levels of IV fluid supply and vasopressor support.

APPENDIX

Calculation of the PRST Score

Index	Condition	Score
Systolic pressure	<Control +10%	0
	<Control + 20%	1
	>Control + 20%	2
Heart rate	<Control +10%	0
	<Control + 20%	1
	>Control + 20%	2
Sweating	Nil	0
	Skin moist to touch	1
	Visible beads of sweat	2
Tears	No excess tears in open eye	0
	Excess of tears in open eye	1
	Tears overflow closed eye	2

Calculation of the PRST score. Adapted from Schwender D, Daunderer M, Klasing S, Mulzer S, Finsterer U, Peter K. Monitoring intraoperative awareness. Vegetative signs, isolated forearm technique, electroencepahlogram and acute evoked potentials. Der Anaesthesist 1196;45:708–21

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