Dosage finding for low-dose spinal anaesthesia using hyperbaric prilocaine in patients undergoing perianal outpatient surgery

V. Gebhardt\(^1\), A. Herold\(^2\), C. Weiss\(^3\), A. Samakas\(^1\) and M. D. Schmittner\(^1\)

\(^1\)Department of Anaesthesiology and Surgical Intensive Care Medicine, University Medical Centre Mannheim, Mannheim, Germany.
\(^2\)Centre of Colo-proctology, Mannheim, Germany and \(^3\)Department of Medical Statistics, University Medical Centre Mannheim, Mannheim, Germany

**Background:** Hyperbaric prilocaine 20 mg/ml may be preferable for perianal outpatient surgery. The aim of this prospective, single-centre, randomised, single-blinded, controlled clinical trial was to determine the optimal dosage of hyperbaric prilocaine 20 mg/ml for a spinal anaesthesia (SPA) in patients undergoing perianal outpatient surgery.

**Methods:** One hundred and twenty patients (18–80 years/ American Society of Anesthesiologists grade I–III) were enrolled in this study. The patients were randomised to receive 10, 20 or 30 mg of prilocaine for SPA. We measured expansion of the sensory and motor block, evaluated times to walk, void and being eligible for discharge, and determined the demand of analgesics.

**Results:** 116/120 patients were available for analysis. The expansion of the sensory block gained with an increasing dosage: 10 mg: 3(1–6) dermatomes; 20 mg: 4(2–6) dermatomes; 30 mg: 5(3–7) dermatomes (\(P < 0.0001\)). Dermatomes were counted upwards beginning with S5. Also, the motor block gained with an increased dosage (Bromage score 1–3: 10 mg: \(n = 3\), 20 mg: \(n = 8\) and 30 mg: \(n = 18\), \(P = 0.0002\)). Patients receiving 10 mg were ready for discharge earlier compared with both other groups (10 mg: 199 ± 39 min; 20 mg: 219 ± 47 min; 30 mg: 229 ± 32 min, \(P = 0.0039\)). Pain occurred earlier in the 10 mg group than in the 30 mg group (10 mg: 168 ± 36 min; 30 mg: 205 ± 33 min, \(P = 0.0427\)). The demand of additional analgesics was comparable in all dosage groups.

**Conclusion:** Hyperbaric prilocaine 20 mg/ml can be applied in dosages of 10, 20 and 30 mg for SPA in perianal surgery. Because of sufficient analgesia, missing motor block and shorter recovery times, 10 mg of hyperbaric prilocaine 20 mg/ml can be recommended for perianal outpatient surgery.

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**Colorectal diseases** are very common among the adult population, their incidence being estimated between 4% and 39%.\(^1\)\(^,\)\(^2\) Roughly 10% of these patients require surgical treatment, and the great majority are performed in an ambulatory setting.\(^3\)\(^,\)\(^4\) Therefore, anaesthesiology plays a key role in facilitating the recovery process in the current outpatient fast-track recovery environment.\(^5\)

Spinal anaesthesia (SPA) with small amounts of hyperbaric local anaesthetics ensures not only a rapid onset of drug action but also a reliable and prolonged analgesia.\(^6\) This method appears to be more efficient than other anaesthesia techniques.\(^7\)\(^,\)\(^8\)

Until recently, only two hyperbaric substances were available in Germany: bupivacaine 5 mg/ml and mepivacaine 40 mg/ml. Both of them have been assessed in several studies;\(^6\)\(^–\)\(^14\) however, in July 2010 a third hyperbaric local anaesthetic, hyperbaric prilocaine 20 mg/ml, was introduced into the market. Compared with mepivacaine, prilocaine seems to have a shorter time of drug action and a lower rate of adverse side effects like transient neurological symptoms (TNS), and may be, therefore, the preferable substance for perianal outpatient surgery.\(^15\)\(^,\)\(^16\) Because of the long drug action, bupivacaine is less feasible for day surgery.

The purpose of this prospective randomised clinical trial was to determine the optimal dosage of hyperbaric prilocaine 20 mg/ml for an SPA in patients undergoing perianal outpatient surgery.
Following our hypothesis, the ‘optimal’ dosage of a hyperbaric substance is defined by a sufficient analgesia during the operative procedure, the absence of a motor block, a minimum length of stay in the clinic due to a fast recovery time and a lower occurrence of side effects such as urinary retention.

**Methods**

In this study, the ‘Sensory block: number of anaesthetised dermatomes counting from the S₅ segment upwards, measured pre-operatively’ was chosen as the primary end point. In addition to a pain-free procedure as the major claim of an anaesthesia, the second outcome parameter was defined as the ‘time until discharge’, representing an optimised working process as well as an increased comfort for our patients.

Sample size calculation has been performed before the study has started by SAS procedure PROC POWER based on the quantitative outcome variable ‘Sensory block: number of anaesthetised dermatomes counting from S₅ upwards, measured pre-operatively’. We assumed in propose that a difference of one dermatome between two groups should be clinically relevant. Assuming a standard deviation of 1.5 (based on experiences with earlier studies of our group), alpha = 0.05 and a power of 0.80, we obtained a total sample size of \( n = 38 \) for each group. Thus, we included 40 patients per group at the beginning of the study.

After obtaining the approval from our local ethics commission (Medical Ethics Commission II, Faculty for Medicine Mannheim, Germany, Nr: 2010-303N-MA) and international registration on http://www.isrctn.org (Nr: 95628829), 120 patients were enrolled into this prospective, single-centre, single-blinded, randomised, controlled clinical trial. From December 2010 until May 2011, verbal and written information was provided to each of the 120 patients before informed written consent was obtained.

**Inclusion and exclusion criteria**

All patients (male/female, American Society of Anesthesiologists physical status I–III, age: 18–80 years) undergoing perianal outpatient surgery were eligible for the study. Exclusion criteria were general contraindications to SPA as well as allergies against diclofenac, metamizole, paracetamol or piritramide. The study protocol permitted the use of general anaesthesia in the case of unsuccessful performance of SPA and incomplete sensory block, resulting in exclusion from the study.

**SPA**

SPA was performed under aseptic conditions using a midline approach. All used local anaesthetics were drawn up under aseptic conditions right before the puncture by the anaesthetist. While the patient was in a sitting position, the L₃-L₄ interspace was identified, and the subarachnoid space was punctured with a 27-G Whitacre pencil-point needle (Becton Dickinson, Madrid, Spain). When cerebrospinal fluid was clear and free-flowing in absence of paraesthesia, the needle was rotated so that the aperture was pointing caudally, and hyperbaric prilocaine 20 mg/ml (Takipril®; Meduna, Aschaffenburg, Germany) was injected as per the randomised dosage. All patients remained in a sitting position for at least 10 min until they were called up for operation and were brought into lithotomy position.

**Patients and procedures**

Before the scheduled operation, all patients were interviewed by an anaesthetist. They received no oral pre-medication. Upon arrival in the day surgery centre, all 120 patients were equally randomised to receive a SPA with 10, 20 or 30 mg, resulting in a volume of 0.5, 1.0 or 1.5 ml of hyperbaric prilocaine 20 mg/ml. Randomisation was made by drawing lots for every single patient out of 120 lots. Venous cannulation with a 20-G peripheral needle was performed in all patients, and infusion with a maximum of 500 ml balanced crystalloid solution (Deltajonin®; AlleMan, Rimbach, Germany) was started. Electrocardiography, non-invasive blood pressure and oxygen saturation were monitored at 5-min intervals throughout the operation (Solar8000®, GE Healthcare, Munich, Germany). Perioperative anaesthesia-related side effects were recorded by a study nurse.

**Testing of sensory block**

The sensory block was tested by the anaesthetist directly after positioning for the procedure and immediately after the operation was completed. Two methods were used for testing the sensory block: haptically with a toothpick and thermally with an ice-filled plastic tube. Pricks were gently applied to the perianal dermatomes with a wooden toothpick and then radially moving outwards in different diagonal directions until the prick felt spiky. In the same way, the skin, then, was gently touched with an...
ice-filled plastic tube until patients felt a temperature difference. The anaesthetised dermatomes were documented. Patients were eligible for the operation when a satisfactory sensory block had reached the S₅ segment at the pre-operative testing.

**Testing of motor block**

The motor block was also assessed in two ways: first, the patient’s ability to transfer themselves with or without assistance from the stretcher where the SPA was applied to the operation table (options: yes/no). Additionally, the motor block was measured by using the modified Bromage score: 0 = no motor block; 1 = unable to lift the extended leg in the hips; 2 = unable to flex hips and knees but still able to flex ankles; 3 = complete motor block of the lower extremity. The motor block was tested after patients were called up for the operation (at least 10 min after intrathecal injection) and immediately when the operation was finished.

**Operative procedures**

If patients pre-operatively requested to sleep during the procedure, propofol 10 mg/ml (Propofol®, Fresenius Kabi, Bad Homburg, Germany) with a maximum dose of 1 mg/kg of body weight was injected until a mild level of sedation was reached, an Observer’s Assessment of Alertness/Sedation score of 4–5. Oxygen was applied at a flow rate of 8 l/min via an oxygen mask, and oxygen saturation, as well as semi-quantitative carbon dioxide detection, was closely monitored to ensure adequate respiration (Primus®, Draeger, Luebeck, Germany).

All procedures were performed on an outpatient basis. Therefore, patients were only suitable if the operation was limited to the perianal skin, the wound not larger than 4 cm × 5 cm and the incision involved no more than one segment of the anus.

**Post-operative procedure and discharge**

After the operational procedure, all patients were transferred to a recovery room for further cardiorespiratory monitoring (Dash3000®, GE Healthcare, Munich, Germany) until the decay of the SPA. In preparation for discharge, light meals and drinks were offered. The time until the first food and drink intake, until spontaneous micturition and until patients were able to get up on their own without any help, were recorded. Patients were eligible for discharge when they reached an Aldrete score of 10, when they were able to get up alone and had voided.

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### Table 1

**Table for the administration of analgesia.**

<table>
<thead>
<tr>
<th>Step</th>
<th>VAS</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0–2</td>
<td>No additional medication</td>
</tr>
<tr>
<td>1</td>
<td>3–4</td>
<td>1000 mg paracetamol or 1000 mg metamizole</td>
</tr>
<tr>
<td>2</td>
<td>5–6</td>
<td>1000 mg paracetamol and 1000 mg metamizole</td>
</tr>
<tr>
<td>3</td>
<td>7–10</td>
<td>1000 mg paracetamol and 1000 mg metamizole and 7.5 mg piritramide</td>
</tr>
</tbody>
</table>

Diclofenac was the only drug given routinely (100 mg suppository at the end of surgery). All other analgesics were given on demand only. When pain was persistent in patients with a VAS score of 7–10, the dosage of piritramide could be increased. VAS, visual analogue scale.

**Analgesics consumption**

As a standard post-operative analgesic regimen, all patients received 100 mg diclofenac (Voltaren®, Novartis Pharma GmbH, Nuremberg, Germany) in the form of suppository at the end of surgery. In the recovery room, additional analgesics were administered according to an appointed analgesia regimen on demand only (Table 1). We assessed the maximum pain experienced using an 11-point visual analogue scale (0, no pain; 10, worst pain imaginable) in case of occurring pain. We documented the occurrence of pain and the amount of analgesics given.

**Statistics**

For statistical analysis, the SAS System (release 9.2; SAS Institute, Cary, NC, USA) was used. Differences between the three dosage groups were tested using a one-way analysis of variance (ANOVA, Kruskal–Wallis test, chi-squared test or Fisher’s exact test, as appropriate. Two unpaired samples were compared by Mann–Whitney U-test or chi-squared test. In order to compare two paired samples, Wilcoxon test has been used.

Quantitative data that are approximately normally distributed are presented as mean values ± standard deviation. The median, together with the range, is given if the data are skewed or ordinally scaled. Test results with P < 0.05 were considered as statistically significant. Data were analysed on an intention to treat basis.

**Results**

One hundred and twenty patients were enrolled during the study period. The performance of SPA
was not possible in four patients (3.3%) because of adverse anatomical conditions, and they received a general anaesthesia. Finally, a total of 116 patients could be included in analysis (10 mg: \( n = 38 \), 20 mg: \( n = 39 \) and 30 mg: \( n = 39 \)).

**Demographic data**

Fifty-eight male and fifty-eight female patients were included. The patients had an average age of 43.3 ± 12.5 years, a body height of 173 ± 9 cm and a body weight of 80 ± 17 kg, resulting in a body mass index of 26.5 ± 4.7 kg/m². The diagnosis, which made surgical treatment necessary, were fissures \( (n = 55) \), condylomas \( (n = 24) \), fistula \( (n = 18) \), haemorrhoids \( (n = 8) \) and others \( (n = 11) \); Table 2).

**SPA**

The performance of the operative procedure in SPA was possible in 114/116 (98.3%) patients. Two patients suffered from pain, both of them received additional medication so that procedures could be finished pain freely. A general anaesthesia was not necessary. One patient received 10 mg of hyperbaric prilocaine 20 mg/ml resulting in a sensory block to the S₁ segment. After insertion of the speculum, the patient claimed to suffer from pain, so she received 0.1 mg of fentanyl and 2 mg of midazolam intravenously. Pain was described more like an unpleasant intestinal discomfort (‘pressure’), not as nociceptive pain.

A second patient with perianal condylomas received 20 mg of hyperbaric prilocaine 20 mg/ml and was pre-operatively tested to have a sensory block to the S₂ segment. For the resection of perianal condylomas, the SPA worked well. Intravaginally located condylomas were found as a random diagnosis during the operation. As the patient received propofol for sedation, the dosage was increased up to 160 mg. Additional analgesics were not necessary.

**Operative procedures**

Twelve patients received propofol 10 mg/ml for sedation. There has been no significant difference regarding dosage groups, dosages of propofol or sex \( (P = 0.2264) \). The procedures were equally distributed in the dosage groups \( (P = 0.8041; \text{Table 2}) \). The mean duration of procedures was 11 ± 5 min; no difference between the dosage groups could be detected (Table 4).

**Sensory block**

The expansion of the sensory block gained with an increasing amount of applied local anaesthetics. The differences between the three dosage groups were highly significant pre- and post-operatively (each \( P < 0.0001; \) Kruskal–Wallis test). There were no statistically significant differences regarding the number of anaesthetised dermatomes pre- or post-operatively measured (Table 3). Both very young and elderly patients were included in the study. So we analysed if the age affects the expansion of the sensory block by using the Spearman correlation coefficients. We could not detect an effect of the age regarding the sensory block expansion (pre-operative: \( r = 0.02592, P = 0.7852 \); post-operative: \( r = 0.02589, P = 0.7922 \)).

**Motor block**

Pre-operatively, the motor block also gained with an increased dosage. Similar results were obtained for the motor block measured post-operatively: There was no statistically significant difference between pre- and post-operative Bromage scores (both 10 and 20 mg: \( P = 0.5000 \); 30 mg: \( P = 1.0000 \)). With an increasing dosage, fewer patients were able to move without help from the stretcher to the operation table and back (Table 3; Fig. 1).

**Recovery times**

The times for voiding and discharge were significantly prolonged with an increasing dosage applied \( (P < 0.0001 \) and \( P = 0.0039 \), respectively; derived by one-way ANOVAs; see Table 4). The discharge times for patients in the 10 mg group were on average about 20 and 30 min earlier compared with the 20 mg and 30 mg group.

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**Table 2**

Demographic data of patients receiving a spinal anaesthesia (SPA) with 10, 20 and 30 mg hyperbaric prilocaine 20 mg/ml. Mean and standard deviation.

<table>
<thead>
<tr>
<th>Dosage of hyperbaric prilocaine 20 mg/ml</th>
<th>10 mg ( (n = 38) )</th>
<th>20 mg ( (n = 39) )</th>
<th>30 mg ( (n = 39) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>21:17</td>
<td>17:22</td>
<td>20:19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.6 ± 12.5</td>
<td>41.3 ± 11.7</td>
<td>41.8 ± 12.8</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>174 ± 8</td>
<td>174 ± 9</td>
<td>171 ± 9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82 ± 17</td>
<td>79 ± 15</td>
<td>77 ± 17</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 ± 4.7</td>
<td>26.2 ± 4.9</td>
<td>26.2 ± 4.5</td>
</tr>
</tbody>
</table>

**Indications**

- Fissures \( 18 \)
- Condyloma \( 6 \)
- Fistula \( 7 \)
- Haemorrhoids \( 1 \)
- Others \( 6 \)

**Operative procedures**

- Excisions \( 19 \)
- Fissurectomy \( 18 \)
- Milligan–Morgan \( 1 \)

BMI, body mass index.
A statistically significant dependence from dosage could not be detected, neither for times for food and fluid intake nor for the occurrence of pain. However, pain occurred earlier in the 10 mg group than in the 30 mg group ($P = 0.0427$, Table 4).

**Analgesics consumption**

39/116 patients announced pain in the recovery room, of that more women than men (43% vs. 24%, $P = 0.0306$). The demand of additional analgesics was comparable in all dosage groups. There has been no significant difference between the groups (Table 3).

**Complications and adverse side effects of SPA**

No life-threatening complications were observed. Hypotonia and bradycardia requiring treatment occurred in 5/116 patients. In all cases, these incidents happened after puncture before application of the local anaesthetics. None of the patients suffered from urinary retention.
Discussion

After the recent introduction of hyperbaric prilocaine 20 mg/ml into the German market, the aim of this current study was to determine the optimal dosage of this substance for patients undergoing minor perianal outpatient surgery. A rising number of ambulatory procedures lead to the development of a safe, reliable and sufficient anaesthesia method for this purpose. Compared with mepivacaine, the alternative, approved, medium long-acting hyperbaric local anaesthetic prilocaine seems to possess a shorter time of drug action and a lower rate of adverse side effects like TNS and may be, therefore, the preferable substance for ambulatory minor colorectal surgery.15,16 The finding of the lowest dosage prilocaine making the surgical procedures possible was the primary outcome parameter.

General aspects of the study

In this study, we could show that even low doses of hyperbaric prilocaine 20 mg/ml provide a safe and sufficient anaesthesia for minor perianal procedures. A limit of this study can be discussed in the lack of information concerning the assessment of TNS. As known from the literature, prilocaine induces by far lower incidences of TNS compared with mepivacaine or lidocaine. In their review article, Eberhart et al. described the incidences for TNS to be 16.9% for lidocaine, 19.1% for mepivacaine but only 1.7% for prilocaine. A similar rate was detected after bupivacaine with 1.1%, but because of the long drug action, bupivacaine is less feasible for day surgery.16 These data are supported by the results of a Cochrane Review. The relative risk to develop TNS after an SPA with mepivacaine or lidocaine compared with other local anaesthetics is claimed to be 7.31.15

Because of this fact, we dispensed with the evaluation of the TNS incidence in our study and focused on dosage finding.

Sensory block and motor block

The performance of SPA was successful in 116/120 patients and showed a comparable rate as in the study of Fuzier with a failure rate of 3.2%, defined as no sensory block.21

In our study, all patients had an adequate sensory block level for perianal surgery. These results are supported by data of Wassef et al. using successfully dosages of 1.5 mg hyperbaric bupivacaine 7.5 mg/ml.6

A motor block can be an unlikely effect of a low-dose SPA. In the 30 mg group, significantly more patients suffered from a motor block compared with the groups with lower dosages.

In a study, Kazak et al. compared 1.5 vs. 6 mg with hyperbaric levobupivacaine 5 mg/ml and found a median Bromage score of 0 for the low-dosage and a score of 1 (range: 1–3) for the high-dosage group.18 Despite the fact that Kazak et al. used another substance, it is remarkable that in the 30 mg group of prilocaine, only 35.1% needed help for positioning compared with 100% of the high-dosage group of the study performed by Kazak et al.18 This fact could indicate a better

<table>
<thead>
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<th>Table 4</th>
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<tbody>
<tr>
<td>Duration of procedures and recovery times.</td>
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</table>

<table>
<thead>
<tr>
<th>Applied dosage of hyperbaric prilocaine 20 mg/ml</th>
<th>10 mg (n = 38)</th>
<th>20 mg (n = 39)</th>
<th>30 mg (n = 39)</th>
<th>P values (ANOVA or t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of procedures</td>
<td>13 ± 7 (5–36)</td>
<td>11 ± 4 (5–20)</td>
<td>11 ± 4 (3–25)</td>
<td>P = 0.3805</td>
</tr>
<tr>
<td>Food and fluid intake</td>
<td>80 ± 23 (45–125)</td>
<td>88 ± 29 (44–160)</td>
<td>102 ± 94 (40–140)</td>
<td>P = 0.5064</td>
</tr>
<tr>
<td>Voiding</td>
<td>173 ± 31 (108–237)</td>
<td>193 ± 38 (90–250)</td>
<td>211 ± 33 (150–289)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Discharge</td>
<td>199 ± 39 (132–341)</td>
<td>219 ± 47 (120–410)</td>
<td>229 ± 32 (166–304)</td>
<td>P = 0.0039</td>
</tr>
<tr>
<td>Pain</td>
<td>168 ± 36 (122–225)</td>
<td>195 ± 47 (120–255)</td>
<td>205 ± 33 (145–255)</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>
mobility even for higher dosages of prilocaine 20 mg/ml compared with other local anaesthetics.

Recovery times
We measured the period of time from intrathecal injection to spontaneous micturition as a necessary precondition for discharge from the day surgery centre. In a study comparing adverse side effects of different hyperbaric local anaesthetics, Hampel et al. found a median time to void from subarachnoid injection of 50 mg of hyperbaric prilocaine 20 mg/ml of 253 min. Rätsch et al. found a time to spontaneous micturition of 306 min and a time to discharge of 308 min using 60 mg of hyperbaric prilocaine 20 mg/ml in patients undergoing lower limb surgery in an ambulatory setting. Also, Camponovo et al. showed earlier voiding and discharge in lower dosages comparing 40 and 60 mg of hyperbaric prilocaine 20 mg/ml (voiding: 195 vs. 218 min, discharge: 208 vs. 256 min). The results of these three studies are according to our data showing that time to void and discharge gains with an increasing dosage. In a previous study, Wassef et al. concluded that a restricted block to the desired area earlier points in time for voiding and ambulation made this dosage more suitable for these procedures in an ambulatory setting.

Analgesics consumption
33.6% of all patients required additional analgesics during their stay in the day surgery centre. While Schmittner et al. found that only 1/101 patients needed additional analgesics in the recovery room when using hyperbaric bupivacaine 5 mg/ml for minor perianal surgery, Rätsch et al. found no difference in patients’ need for additional analgesics comparing the hyperbaric substances prilocaine 20 mg/ml and bupivacaine 5 mg/ml for SPA. Although there is no significant difference, it is catching one’s eyes that fewer people announce pain in the 10 mg group compared with both higher dosage groups. We had a closer look on that issue, but we could not detect any correlation explaining this finding.

Complications and adverse side effects of SPA
In this study, five patients (4.3%) suffered from bradycardia and hypotension, but all before prilocaine was administered intrathecally. In earlier studies of our group, we found rates between 2% and 2.8%. Kazak et al. found a rate of 0%. The missing oral premedication may explain this phenomenon.

Conclusion
Hyperbaric prilocaine 20 mg/ml can safely be applied in dosages of 10, 20 and 30 mg for SPA in colorectal surgery. Because of sufficient analgesia, missing motor block and shorter recovery times, 10 mg of hyperbaric prilocaine 20 mg/ml can be recommended for perianal outpatient surgery. Procedures should be limited to the perianal skin, the wound should not be larger than 4 × 5 cm and the incision should not involve more than one segment of the anus, as well as the procedure should not last longer than 40 min.

Conflicts of interest: M. Schmittner received payments and travel funding for presenting parts of the study at the Annual Congress of the European Society of Regional Anaesthesia in Dresden, Germany (September 2011), at the Annual Congress of the German Society for Coloproctology in Munich, Germany (March 2012), at the Annual Congress of the German Society for Surgery in Berlin, Germany (April 2012) and at the Annual Congress of the German Society for Anaesthesiology in Leipzig, from Sintetica, Switzerland and Meduna, Aschaffenburg Germany (May 2012); V. Gebhardt received travel funding for presenting parts of the study at the ‘Hauptstadtkongress für Anästhesie und Intensivmedizin’ of the German Society for Anaesthesiology in Berlin, Germany (September 2011) from Meduna, Switzerland.; A. Herold: no conflicts of interests; C. Weiss: no conflicts of interests; A. Samakas: no conflicts of interests.

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Address:
Marc D. Schmittner
Department of Anaesthesia and Surgical Intensive Care Medicine
University Medical Centre Mannheim
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
Germany
e-mail: marc.schmittner@umm.de

Supporting Information
Additional Supporting Information may be found in the online version of this article:
Appendix S1. CONSORT diagram.