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Spinal hyperbaric prilocaine vs. mepivacaine in perianal outpatient surgery

Research Article

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Abstract: Background. The aim of this randomised, clinical trial was to compare safety and efficiency of hyperbaric prilocaine and mepivacaine at a dosage of 0.5 ml each for perianal outpatient surgery in terms of transient neurologic symptoms (TNS) and postoperative recovery. Methods. 160 patients aged 18-80 years were randomized to receive a spinal anaesthesia (SPA) with 0.5ml of mepivacaine or prilocaine. We measured the expansion of the block, evaluated postoperative recovery times and determined the incidence of TNS one week after surgery. Results. 160 patients (93 male / 67 female) were available for analysis. Prilocaine led to shorter times from SPA to micturition (prilocaine: 178 (110-254) min vs. mepivacaine: 195 (130-305) min, $p=0.0008$) and discharge (prilocaine: 192 (126-267) min vs. mepivacaine: 220 (140-320) min, $p<0.0001$). 152 / 160 patients were available for the telephone follow-up. Six patients (9%) receiving mepivacaine compared to zero patients of the prilocaine group announced typical symptoms of TNS ($p=0.0284$). Conclusion. Both, hyperbaric mepivacaine 40 mg/ml and hyperbaric prilocaine 20 mg/ml can be used at a dosage of 0.5 ml each for SPA in perianal outpatient surgery. Due to the faster recovery profile and a lower incidence of TNS, we recommend the use of 10mg hyperbaric prilocaine 20 mg/ml for this indication.

Keywords: *Prilocaine • Mepivacaine • Transient neurologic symptoms • Anaesthesia • Spinal • Ambulatory surgical procedures • Colorectal surgery*

1. Introduction

Spinal anaesthesia (SPA) is a reliable anaesthetic technique for ambulatory surgery [1]. For this purpose, local anaesthetics with a pharmacokinetic profile fitting the special requirements of an outpatient setting are necessary. They should provide a rapid onset, a suitable duration of sensory block as well as a rapid recovery from motor block and should be associated with minimal side effects [2].

The use of lidocaine for SPA in outpatient care was largely abandoned due to a relatively high incidence of transient neurologic symptoms (TNS). These symptoms appear as pain or abnormal sensations in the gluteal region and the lower extremities within 24h after an uneventful SPA, last for 1-3 days and disappear without sequelae [3-5]. Hyperbaric mepivacaine was initially a promising alternative. But shortly thereafter, the incidences for TNS for mepivacaine and lidocaine were shown to be nearly similar [3,6]. However, until the introduction of hyperbaric prilocaine 20 mg/ml into the

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German market in the year 2010, there has been no alternative approved hyperbaric local anaesthetic with a comparable pharmacokinetic profile. Nevertheless, mepivacaine is still being used especially for outpatient SPA due to its short duration of action and lower costs. There is evidence that TNS caused by lidocaine is neither dose- nor concentration-dependent but represents a more substance-related adverse side effect [7,8]. So far, no study examined the incidence of TNS using very low doses of spinal mepivacaine and prilocaine. We compared both substances' exemplarily for ambulatory colorectal surgery, where low-dose SPA has been found superior compared with general anaesthesia [9,10]. The aim of this study was to compare safety and efficiency of the new preparation of hyperbaric prilocaine 20 mg/ml to hyperbaric mepivacaine 40 mg/ml in terms of incidence of TNS and postoperative recovery.

2. Methods

After approval from the local ethics commission (Medical Ethics Commission II, Mannheim, Germany; Vote number: 2011-298N-MA, 20.07.2011) and international registration (www.isrctn.org, registration number: 15303706), 160 patients were enrolled to this prospective, randomized, single-blinded, single-centre, clinical trial. From July 2011 until May 2012, verbal and written information were given to each of the 160 patients before informed written consent was obtained.

3. Inclusion and exclusion criteria

All patients (male/female; aged 18-80 years, American Society of Anesthesiologists physical status I-III) undergoing perianal outpatient surgery were eligible for the study. Exclusion criteria were general contraindications against SPA and allergies against substances used. The study protocol permitted the use of general anaesthesia in the case of unsuccessful or incomplete SPA, resulting in exclusion from the study. All procedures were performed on an outpatient basis. Therefore, patients were only suitable if the operation was limited to the perianal skin, the wound was not larger than 4 x 5 cm and the incision involved no more than one segment of the anus.

4. Patients and procedures

An anaesthesiologist interviewed all patients before the scheduled operation. All 160 patients were equally randomized to receive either 20mg hyperbaric mepivacaine 40mg/ml or 10mg hyperbaric prilocaine 20mg/ml, resulting in a volume of 0.5ml each, for SPA.

Randomization was carried out by computerized block randomization. Venous cannulation with a 20-gauge peripheral needle was performed and infusion with a maximum of 500 ml balanced crystalloid solution (Deltajonin ®, AlleMan, Rimbach, Germany) was started. Electrocardiography (ECG) and oxygen saturation were continuously monitored, non-invasive blood pressure was measured at 5-min intervals throughout the operation (Solar8000, GE Healthcare, Munich, Germany). Potential perioperative anaesthesia-related side effects were recorded by a study nurse. Anaesthesia and surgery times were determined according to the German Society of Surgery and the German Society of Anaesthesiology [11].

5. Spinal anaesthesia

Patients received no oral premedication but in the case of anxiety, 2 mg midazolam (Midazolam-hameln ®, Hameln pharmaceuticals, Hameln, Germany) were administered intravenously. SPA was performed under aseptic condition using a standard midline approach in the sitting position. The puncture of the subarachnoid space was performed at the L3-L4 interspace with a 27-gauge Whitacre pencil-point needle (Becton Dickinson, Madrid, Spain) and 10mg hyperbaric prilocaine (Takipril ®, Meduna, Aschaffenburg, Germany) or 20mg hyperbaric mepivacaine (Scandicain 4% hyperbar ®, Astra Zeneca, Wedel, Germany) were injected as per randomisation. All patients remained in the sitting position for at least 10 minutes until they were brought into lithotomy position for surgery. In case of a difficult puncture the protocol permitted the use of a 25-gauge needle or a change of the interspace.

6. Testing of sensory and motor block

To minimize the bias of a single-blinded study, a study nurse who was not involved in the process of randomization and administration of the local anaesthetic tested the sensory and the motor block >10 minutes after intrathecal injection when the patient was in lithotomy position.

For sensory block, 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. The anaesthetized dermatomes

were documented. Patients were eligible for surgery when a sensory block had reached the S5 segment.

We assessed the motor block 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) [12,13].

7. Operative procedures

When patients preoperatively decided to sleep during intervention, propofol (Propofol ®, Fresenius Kabi, Bad Homburg, Germany) was injected at a maximum dose of 1 mg/kg of body weight until a mild level of sedation was reached, an Observer´s Assessment of Alertness/ Sedation score of 4-5 [14]. Oxygen was applied at a flow rate of 8 L/minute via an oxygen mask and oxygen saturation as well as semiquantitative carbon dioxide detection was closely monitored to ensure adequate respiration (Primus ®, Draeger, Luebeck, Germany).

8. Postoperative procedure and discharge

All patients were transferred to a postanaesthetic care unit (PACU) for further cardio-respiratory monitoring (Dash3000 ®, GE Healthcare, Munich, Germany) after the surgical procedure until the decay of the SPA. A study nurse recorded the time spans until first spontaneous micturition, ability to get up and walk without assistance and discharge. Patients were eligible for discharge when they reached an Aldrete score of ≥18, when they were able to get up alone and had voided [15].

9. Analgesics consumption

All patients received 100mg diclofenac (Voltaren ®; Novartis Pharma, Nuremberg, Germany) in suppository form at the end of surgery. In the recovery room, additional analgesics were administered according to an appointed analgesia regimen on demand only (Figure 1). We assessed the maximum pain experienced using an 11-point visual analogue scale (VAS; 0, no pain; 10, worst pain imaginable) and documented the amount of applied analgesics. Patients received diclofenac 2 x 75 mg per os for five days as basic analgesia scheme after discharge.

10.TNS

One week after surgery a telephone call follow-up was performed to evaluate the incidence of TNS according to the definition in Table 1. In case of patients´ inaccessibility over a period of two weeks after surgery, patients were excluded from the follow-up analysis.

Table 1. Transient neurologic symptoms (TNS); these symptoms were used to detect TNS during the telephone interview and to differentiate them from usual back pain [3,5,6]

Transient neurologic symptoms (TNS)	
Occurrence	within 24 h after an uneventful SPA
Pain	moderate to severe (VAS 3-8), described as dull
Symptoms	abnormal sensations, hypoesthesia or dysesthesia in the gluteal region, radiating to the lower extremities
Duration	1-3 days, no residuum

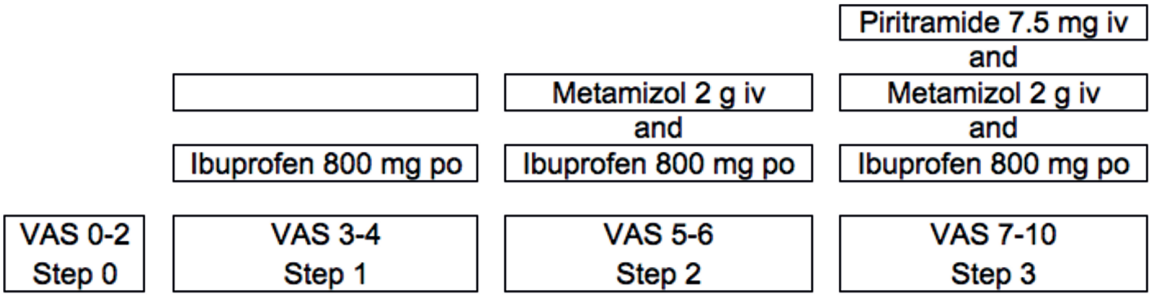

Figure 1. Step diagram for the administration of analgesics. Diclofenac was the only drug given routinely (100 mg in form of a suppository at the end of surgery). All other analgesics were given on demand only. When the pain was persistent in patients with a visual analogue scale (VAS) score of 7-10, the dosage of piritramide could be increased.

11. Statistics

As we felt the safety and therefore the incidence of TNS as the main aspect for the choice between two substances with nearly similar pharmacological characteristics, we have chosen the incidence of TNS as the main objective of this study. We performed a power analysis according to the Cochrane review of Zaric and Pace [3] assuming 0.2 % for prilocaine and 10 % for mepivacaine as TNS proportions. With alpha = 0.05 and power = 0.80 we assessed a total sample size of 156. Thus, we included 80 patients by randomization in each group.

To proof the efficiency of the new preparation of prilocaine, secondary objectives were the expansion of sensory and motor block, times until patients were able to walk and void, the occurrence of pain after the procedure and finally the time until discharge.

For qualitative parameters, absolute and relative frequencies are given; quantitative variables approximately normally distributed are presented by their mean values and standard deviations. Time durations are characterized by median values together with minimum and maximum.

To compare two groups regarding a nominal scaled parameter, Chi2 – test or Fisher's exact test has been performed, as appropriate. For ordinal scaled parameters, Cochran-Armitage trend test has been used. Measures of location were compared by 2 sample *t*-tests (for normally distributed data) or Mann-Whitney-U-tests. Test results with $p < 0.05$ were considered as statistically significant. All statistical calculations have been done with the SAS system, release 9.2 (SAS Institute Inc., Cary, NC, USA).

12. Results

A total of 160 patients were enrolled during the study period (prilocaine: n=80; mepivacaine: n=80). The performance of SPA was possible in all 160 patients who were included in analysis. 152 / 160 patients (prilocaine: n=76 and mepivacaine: n=76) were available for the telephone call follow-up. Eight patients were excluded from the follow-up analysis due to inaccessibility.

13. Demographic data

93 male and 67 female patients were included in the study. Although the body weight was higher in patients receiving mepivacaine, the body mass index was comparable in both groups (Table 2).

14. Spinal anaesthesia

In 22 / 160 patients (13,75%) more than one puncture was necessary for successful SPA without a difference between the groups (prilocaine: n=10 vs. mepivacaine: n=10, p=0.8477). The numbers of patients receiving 2 mg midazolam intravenously for sedation before puncture were similar in both groups (prilocaine: n=11 vs. mepivacaine: n=11, p=0.8477).

15. Sensory and motor block

The median (range) expansion of the sensory block measured before surgery was comparable in both groups (prilocaine: S2 (S5-L4) vs. mepivacaine: S2 (S4-L4), p=0.0038). A motor block (Bromage Score: 1) occurred in 1/80 patients of the mepivacaine group whereas all 80 patients of the prilocaine group had a Bromage Score of 0 (p=1.0).

16. Operative procedures

The operative procedures were performed free of pain in all 160 patients. 38 patients with prilocaine and 39

Table 2. Demographic data of patients receiving a spinal anaesthesia with prilocaine or mepivacaine. *Values are mean ±SD; BMI, body mass index; ASA, American Society of Anaesthesiologists

	Prilocaine (n=80)	Mepivacaine (n=80)	P
Sex ratio (M:F)	44 : 36	49 : 31	0.4230
Age (years)*	42.3 ±12.8	41.3 ±12.5	0.6053
Body height (cm)*	173,8 ± 9,6	171.7 ±8.5	0.1447
Body weight (kg)*	73.7 ±13.9	79.0 ±17.3	0.0366
BMI (kg/m²)*	24.9 ±3.5	26.0 ±4.5	0.0840
ASA (1:2:3)	59 : 21 : 0	57 : 20 : 3	0.4245
Operative procedure Excision : Fistulectomy : Abscess drainage	74 : 5 : 1	75 : 4 : 1	1.0

patients with mepivacaine received propofol for intraoperative sedation (p=1.0). There was no statistically significant difference between the groups concerning the time from SPA until the beginning of surgery (Table 3).

17. Postoperative procedures, discharge and analgesics consumption

Although patients of both groups had comparable times until mobilization, prilocaine led to shorter time spans until first spontaneous micturition. No patient needed urinary catheterization. Times until discharge were also significantly shorter in the prilocaine group (Table 3).

60 patients (prilocaine: n=29 vs. mepivacaine: n=31, p=0.7440) suffered from pain in the PACU. The application of prilocaine led to an earlier announcement of pain compared to mepivacaine (prilocaine: 173 (110-235) min vs. mepivacaine: 185 (108-306) min, p=0.0479) but the number of analgesics did not differ between the groups (Tables 3 and 4).

18. TNS

When patients were recalled for typical symptoms of TNS one week after surgery, six patients (9%) who had received mepivacaine compared to zero patients of the prilocaine group stated that they had suffered from TNS for a few days after SPA (p=0.0284). Table 5 gives details of the patients announcing TNS.

19. Discussion

In this study we demonstrated that the use of hyperbaric prilocaine is advantageous compared with hyperbaric mepivacaine for SPA in patients undergoing perianal outpatient surgery. This fact is caused by shorter recovery times and a significantly lower rate of TNS.

In 1993, transient neurologic toxicity was described in patients recovering from single injection with lidocaine [16]. The cause of this painful complication is as yet unknown and none of the speculations on its origin have been substantiated [3]. Previous studies indicated TNS to be a substance-specific effect, neither concentration nor dose dependent [7,8]. Nevertheless, the incidence of TNS has never been investigated in very low doses of local anaesthetics for spinal anaesthesia. In our study, the low dose of 20 mg mepivacaine resulted in a TNS rate of 9% compared to 0% in the prilocaine group.

In a review article Eberhart and colleagues found the incidence of TNS after intrathecally injection to be 19.1 (0-36.7)% for mepivacaine and only 1.7 (0-4)% for prilocaine [5]. These findings were confirmed by a Cochrane Review performed by Zaric and Pace in 2009 [3]. The authors reported the frequency of TNS and neurologic complications after SPA with lidocaine compared to other local anaesthetics; the relative risk for developing TNS after SPA with lidocaine as compared to other local anaesthetics was 7.31. Mepivacaine was found to give similar high results as lidocaine. The incidence of TNS in our study is high compared with previous studies and reviews, although we used very low doses of the local anaesthetics. These findings improve the assumption that TNS is a substance specific effect.

Once more, this study demonstrates that low-dose SPA is a safe and reliable technique with a high success

Table 4. Analgesic consumption in the PACU. Analgesics were applied according to the step diagram for the administration of analgesics (Figure 1), po = per os, iv = intravenously, p = 1.0 (Cochran-Armitage trend test)

	Prilocaine (n=80)	Mepivacaine (n=80)
Step 0: no analgesics	54	51
Step 1: Ibuprofen 800 mg po	21	24
Step 2: Ibuprofen 800 mg po + Metamizol 2 g iv	2	5
Step 3: Ibuprofen 800 mg po + Metamizol 2 g iv +Piritramide 7.5 mg iv	3	0

Table 3. Duration of anaesthesia and postoperative events. Values are median (range). *time from first incision to last surgical procedure; #time from entering PACU to attainment of an Aldrete score of ≥18, leading to discharge; SPA, spinal anaesthesia.

	Prilocaine (n=80)	Mepivacaine (n=80)	p
Time from SPA until begin of surgery (min)	55 (26-134)	56.5 (18-102)	0.9538
Surgery time * (min)	9.5 (3-26)	9.5 (2-21)	0.8237
Recovery room time # (min)	117 (30-220)	149.5 (63-255)	< 0.0001
Time to first mobilization (min)	168 (98-252)	175 (100-300)	0.0826
Time to announcement of pain (min)	173 (110-235)	185 (108-306)	0.0479
Time to first micturition (min)	178 (110-254)	195 (130-305)	0.0008
Time to discharge (min)	192 (126-267)	220 (140-320)	< 0.0001

Table 5. Details of patients suffering from transient neurologic symptoms (TNS).

Patient Nr	sex	Age (years)	diagnosis	Onset of TNS *	End of TNS *	Radiating to	VAS
1	M	29	Fibroma	1	3	Calves	5
2	M	40	Fissure	1	4	Legs	3
3	M	40	Condyloma	1	3	Gluteal	4
4	M	44	Condyloma	1	4	Gluteal	3
5	F	21	Fissure	2	5	Gluteal	4
6	M	23	Condyloma	1	3	legs	3

** day(s) after surgery; VAS, maximum pain experienced using an 11-point visual analogue scale (VAS; 0, no pain; 10, worst pain imaginable)*

rate and supports previous findings of other authors [12,13,17,18]. Despite these findings, the application of small doses hyperbaric local anaesthetics is discussed controversially [19]. Even though the puncture was described difficult in 22 cases (13,75%), patients of both groups had a sufficient sensory block level of S5 or higher with unrestricted mobility. Fuzier et al. published a failure rate of 3.2% for SPA defined as insufficient or no block [20].

Camponovo et al. compared hyperbaric prilocaine 20mg/ml in doses of 40 and 60 mg with 60 mg of plain prilocaine 20mg/ml [21]. 29/30 patients with 40mg hyperbaric prilocaine achieved a T10-level sensory block after spinal injection and had a mean time ± SD to unassisted ambulation of 92 ± 36 min, a time to void of 195 ± 60 min and a time to eligibility for discharge of 208 ± 68 min. The use of 20 mg in our study vs. the 40 mg prilocaine in the study of Camponovo et al. led only to a reduction of time to voiding and discharge < 20 min. Nevertheless, perianal surgery *per se* was identified as an independent risk-factor for delayed discharge caused by prolonged time until spontaneous micturition [22].

O´Donnell et al. tested whether isobaric mepivacaine 30mg along with fentanyl 10µg provides adequate SPA with shorter duration of functional motor block as compared with isobaric mepivacaine 40mg alone in ambulatory knee surgery [23]. They found that the mepivacaine + fentanyl group provided a faster block regression leading to an earlier ambulation (176 ± 40.3 min) compared with the mepivacaine group. Although we used only 20mg hyperbaric mepivacaine, the patients had a nearly identical time to first mobilization of 175 (100-300) min.

Two studies investigated urinary retention rates in patients receiving 50 mg and 60 mg hyperbaric prilocaine and found rates of 8.3% and 25% [24,25]. It seems that low dose SPA as used in our study does not cause urinary retention, especially when prilocaine is used.

One general limit of this study may be mentioned: the anaesthesiologist was not blinded in regard of the substance used. We minimized this bias by instructing a study nurse to test the block height and apply analgesics in the PACU. In a former trial, our research group investigated hyperbaric prilocaine 20 mg/ml for perianal outpatient surgery and found 10mg the preferable dosage, representing a volume of 0.5 ml [17]. Hyperbaric mepivacaine is commercially available only in a concentration of 40mg/ml. Following a review article by Greene, the spread of anaesthesia is more dependent on the volume than on the concentration of hyperbaric local anaesthetics, especially when applied in a sitting position [26]. Therefore, and to improve the generalizability of the results, we decided to compare both substances in equal volume, 0.5 ml each, taking into account different doses of both local anaesthetics. Although studies comparing different concentrations of lidocaine, whose pharmacokinetic profile is widely similar to mepivacaine, showed no difference in question of block duration, the higher concentration of mepivacaine may be one factor leading to the longer duration of stay [7,27]. A further explanation of this finding may be the different pharmacological properties, leading to a longer block duration for mepivacaine compared with prilocaine [28].

20. Conclusion

Both mepivacaine 40mg/ml and prilocaine 20mg/ml are hyperbaric local anaesthetics that can be used at a dosage of 0.5 ml each for SPA in perianal outpatient surgery. Due to a faster recovery profile and a lower incidence of TNS, we recommend the use of 10 mg hyperbaric prilocaine 20 mg/ml for this indication.

Funding and conflict of interests

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