Effect of Thoracic Epidural Ropivacaine *versus* Bupivacaine on Lower Urinary Tract Function

A Randomized Clinical Trial

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ABSTRACT

Background: Thoracic epidural analgesia with bupivacaine resulted in clinically relevant postvoid residuals due to detrusor underactivity. This study aimed to compare the risk of bladder dysfunction with ropivacaine *versus* bupivacaine using postvoid residuals and maximum flow rates. Our hypothesis was that ropivacaine would result in lower postvoid residuals, because ropivacaine has been shown to have less effect on motor blockade.

Methods: In this single-center, parallel-group, randomized, double-blind superiority trial, 42 patients undergoing open renal surgery were equally allocated to receive epidural bupivacaine 0.125% or ropivacaine 0.2%, and 36 were finally included. Inclusion criterion was normal bladder function. Patients underwent urodynamic investigations preoperatively and during thoracic epidural analgesia. Primary outcome was the difference in postvoid residual preoperatively and during thoracic epidural analgesia postoperatively. Secondary outcomes were changes in maximum flow rate between and within the groups.

Results: Median difference in postvoid residual (ml) from baseline to postoperatively was 300 (range, 30 to 510; $P < 0.001$) for bupivacaine and 125 (range, −30 to 350; $P = 0.011$) for ropivacaine, with a significant mean difference between groups (−175; 95% confidence interval −295 to −40; $P = 0.012$). Median difference in maximum flow rate (ml/s) was more pronounced with bupivacaine (−12; range, −28 to 3; $P < 0.001$) than with ropivacaine (−4; range, −16 to 7; $P = 0.025$) with a significant mean difference between groups (7; 95% confidence interval 0 to 12; $P = 0.028$). Pain scores were similar. No adverse events occurred.

Conclusions: Postvoid residuals were significantly lower using ropivacaine compared to bupivacaine for thoracic epidural analgesia reflecting less impairment of detrusor function with ropivacaine. **(ANESTHESIOLOGY 2017; XXX:00-00)**

POSTOPERATIVE urinary retention is common with a reported incidence of 5 to 70%.[1] It is linked to several factors including type of surgery, preexisting neurologic disease, increased age, increased intravenous fluid administration, postoperative pain, and use of opioids and neuraxial anesthesia.[1] The treatment of choice is bladder catheterization, which is associated with relevant morbidity (patient discomfort, urethral trauma, urethral stricture, and urinary tract infections). The risk of urinary tract infection with a single catheterization is 1 to 2% and can rise by 5 to 10% for every additional day with an indwelling catheter.[2] It is the most common nosocomial infection in the United States, accounting for more than 1 million cases each year and 900,000 additional hospital days/yr. Urinary tract infections are directly responsible for 13% of deaths related to nosocomial infections[3] and are associated with high financial implications.[4]

Thoracic epidural analgesia (TEA) has been shown to provide the most effective analgesia as well as to facilitate postoperative rehabilitation after major thoracic or abdominal surgery.[5] TEA with bupivacaine alone or in combination with fentanyl or with fentanyl and epinephrine significantly inhibits detrusor function, which in turn results in clinically relevant postvoid residual urine volume (PVR), which requires monitoring or catheterization.[6–8] Ropivacaine, on the other hand, administered in the lumbar epidural space during labor, affects motor blockade of the lower extremities to a clinically relevant lesser degree than bupivacaine. Thus, the two local anesthetics may have different effects on

What We Already Know about This Topic

- Epidural analgesia can provoke bladder dysfunction
- Whether there is less urinary retention with ropivacaine than bupivacaine remains unknown

What This Article Tells Us That Is New

- Postvoid bladder volume was less with ropivacaine than bupivacaine, and urine flow was better maintained
- Ropivacaine is preferable to bupivacaine for bladder function and may prevent catheterization in some patients

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bladder function.[9] However, the analgesic potency of ropivacaine is approximately 60% of that of bupivacaine.[10]

The objective of this study was to investigate the effect of ropivacaine in the thoracic epidural space on bladder function and compare it to the effect of equianalgesic doses of bupivacaine. The hypothesis being that ropivacaine would have less impact on bladder function, assessed by PVR and urodynamic investigations.

Materials and Methods

Ethics

This single-center, randomized, double-blind, parallel-group interventional superiority study was approved by the local ethics committee of the University Hospital of Bern (KEK Bern, Switzerland, KEKBE 390/14), prospectively registered at ClinicalTrials.gov (NCT02414373, principal investigator P. Y. Wuethrich, date of registration: March 26, 2015) and conducted in compliance with the Declaration of Helsinki and good clinical practice. Full trial protocol can be accessed on request. All patients gave preoperative written informed consent to participate.

Study Design and Patients

Patients planned for open renal surgery were screened for inclusion at the Department of Urology of the University Hospital of Bern, Bern, Switzerland. All recruited patients completed the validated International Prostate Symptom Score questionnaire.[11] Only patients with no preexisting lower urinary tract symptoms (Internationale Prostate Symptom Score less than or equal to 7) and a PVR less than 100 ml (assessed by ultrasound) were included after providing written informed consent.[12] Exclusion criteria were any contraindication to TEA and pregnancy (exclusion for surgery *per se*).

Forty-two patients were equally randomly allocated to either TEA with bupivacaine 0.125% or ropivacaine 0.2% by a computer-generated randomization list without blocking, following the recommendation of the Consolidated Standards of Reporting Trials statements. The allocation sequence was prepared by an independent operator not involved in the study, and the allocation assignment was concealed in opaque sealed envelopes that were sequentially numbered. Patients were allocated to the treatment group by assigning them the sequentially numbered envelope with the lowest number. Patients and investigators of bladder function were blinded to the epidural solution administrated; the contents of the epidural mixture were not distinguishable because the vials were placed in a sealed opaque bag by an anesthesiologist not involved in the study before patient and investigator entered the urodynamic room.

Time Course and Intervention

After recruitment, the first (baseline) urodynamic investigation was performed without TEA the day before surgery. Urodynamic investigations were performed according to good urodynamic practice.[13] After placement of a 6 French transurethral dual channel catheter (B. Braun Medical, Germany) and a 14 French rectal balloon catheter (Gaeltec, United Kingdom), the bladder was filled at a rate of 25 to 50 ml/min with Ringer's lactate solution at room temperature. The rectal catheter measures rectal, *i.e.*, intraabdominal, pressure. Detrusor pressure is calculated by subtracting the intraabdominal pressure from the intravesical pressure resulting (*e.g.*, during coughing) in the pressure increase produced by the detrusor muscle itself (detrusor pressure).[13] Parameters of both the storage phase (bladder volume at first desire to void, bladder volume at strong desire to void, maximum cystometric capacity (maximum filling volume), bladder compliance (relationship between change in bladder volume and change in detrusor pressure), and voiding phase (maximum detrusor pressure, detrusor pressure at maximum flow rate, maximum flow rate, and PVR were recorded (fig. 1). An Aquarius XT multichannel urodynamic system was used for all measurements (Laborie Medical Technologies Corp., Canada). The methods, definitions, and units accord with the standards recommended by the International Continence Society.[14]

All patients received a thoracic epidural catheter placed at the interspace T7–8 or T8–9 before induction of anesthesia. The insertion site was determined using the classic landmark method, whereby the spinal process of T7 was identified at the line intersecting the inferior tip of the scapulae in the sitting position. An 18-gauge epidural needle was inserted by a paramedian or median approach, and the epidural space was identified with the loss-of-resistance technique. A test dose of 1.5 ml of lidocaine 20 mg/ml with 0.005 mg/ml epinephrine was given to rule out subarachnoidal or intravascular placement.

TEA was then activated 20 min before skin incision with bupivacaine 2.5 mg/ml at a rate of 6 to 10 ml/h in both groups during surgery. No opioids were administrated epidurally during surgery. General anesthesia was induced with propofol, fentanyl, and rocuronium and maintained with isoflurane. A transurethral catheter was inserted after induction and left in place until the next urodynamic investigation. At the end of surgery, continuous epidural analgesia was maintained with the epidural drug according to the randomization: bupivacaine 1.25 mg/ml (bupivacaine group) (bupivacain 0.125% Bioren; Sintetica–Bioren, Switzerland) or ropivacaine 2 mg/ml (ropivacaine group; naropin 0.2% Sintetica; Sintetica–Bioren) using a CADD Legacy ambulatory infusion pump (model 6300; Deltec Inc., USA). The initial infusion rate was 8 ml/h, with additional bolus volumes of 5 ml (lockout time: 1 h). Higher concentrated ropivacaine was used to reach equipotent analgesia because analgesic potency of ropivacaine is approximately 60% of that of bupivacaine.[10]

The infusion rate was then adapted if necessary based on assessments made every 4 h to maintain a pain intensity

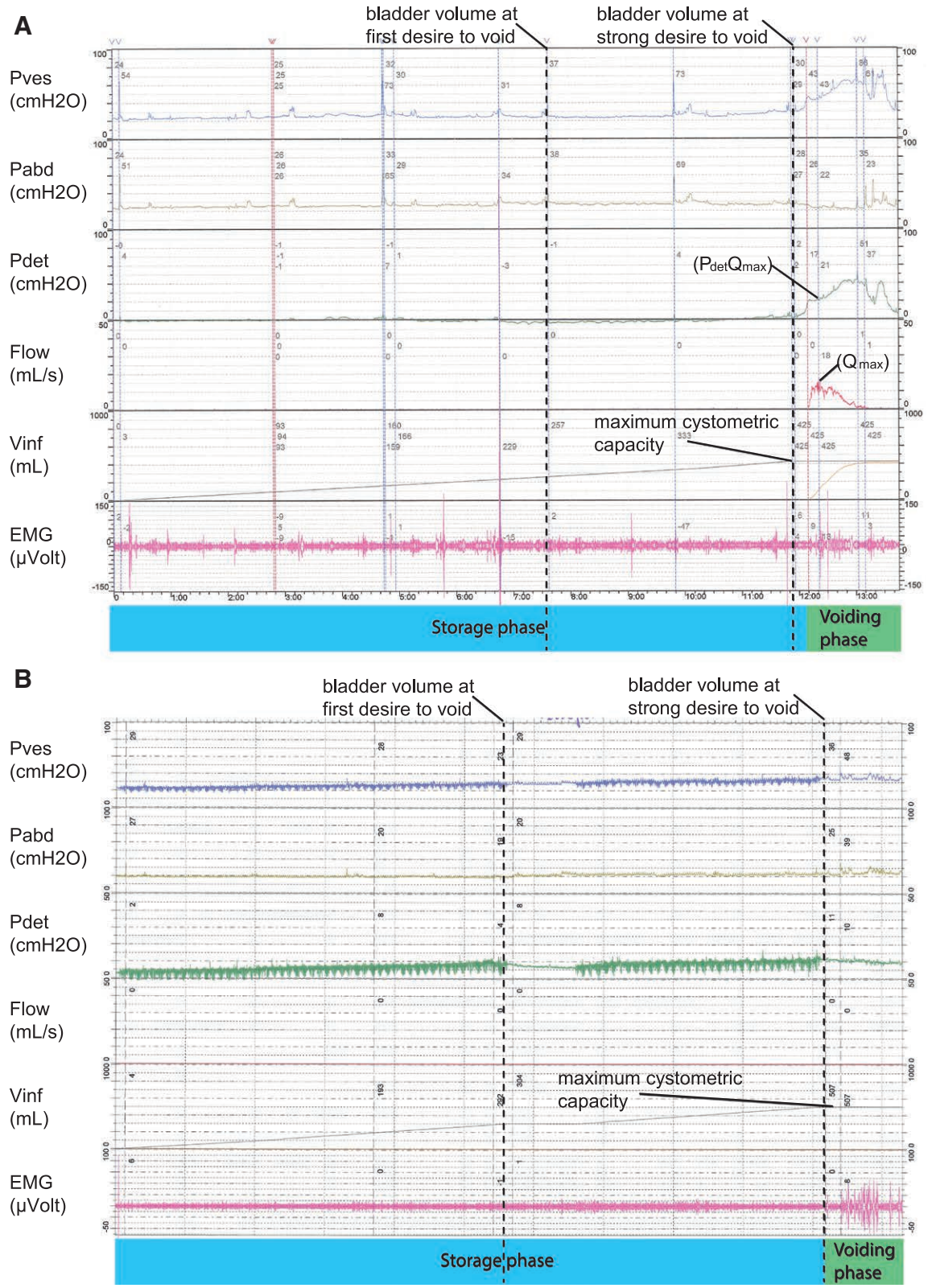

Fig. 1. (*A*) Example of a representative urodynamic tracing from a study patient showing one micturition at baseline. An electromyography (EMG) shows tracing taken from the pelvic floor muscles by perianal surface electrodes. (*B*) A representative urodynamic tracing from a study patient showing one micturition cycle during thoracic epidural analgesia postoperatively with urinary retention due to detrusor muscle underactivity. Flow = voided urine measured on the scale over time; Pabd = intraabdominal pressure (measured by the rectal balloon); Pdet = detrusor pressure (calculated as difference from Pves – Pabd); PdetQmax = detrusor pressure at maximum flow rate; Pves = intravesical pressure; Qmax = maximum flow rate; Vinf = filling of the bladder.

lower than 3 at rest and lower than 5 during mobilization on the numeric rating scale (NRS), in which 0 = no pain and 10 = worst pain imaginable. The maximum infusion rate was 15 ml/h. Additional rescue analgesia with a systemic administration of opioids (fentanyl) was permitted if the NRS was defined as a NRS of more than 5 after optimization of the TEA.

The level of sensory blockade was assessed by hyposensitivity to cold. A cold gel bag (Nexcare reusable cold pack; 3M, USA) with a surface of 4 cm^2 was applied for 1 s to each dermatome.[15]

The second urodynamic investigation was performed on the second or third postoperative day around noon, depending on the patient's mobilization. Patients were mobilized the evening after surgery (bedside mobilization) and then were encouraged to ambulate on postoperative day 1 (short walk on the ward). Segmental blockade was assessed at 8:00 AM, and if necessary, the epidural mixture rate was optimized to achieve a segmental blockade above T6 and below T10, not exceeding T12 bilaterally. Potential risk factors for postoperative urinary retention (postoperative rescue opioid requirement, postoperative nausea and vomiting, sedation) were also documented.

Endpoints

The primary endpoint was within-patient difference (Δ) in PVR (Δ = value during TEA postoperatively – baseline value) between the two groups. Secondary endpoints were within-patient difference in bladder volume at first desire to void, bladder volume at strong desire to void, maximum cystometric capacity, bladder compliance, maximum detrusor pressure, detrusor pressure at maximum flow rate, maximum flow rate, PVR between the time points (during TEA postoperatively *vs*. baseline), and postoperative pain scores according to the NRS. The bladder contractility index, which reflects the strength of the detrusor contraction, was calculated according to the formula "detrusor pressure at maximum flow rate plus 5 maximum flow rate." Bladder voiding efficiency, the product of bladder contractility against urethral resistance, was defined as the percentage of voided volume/maximum cystometric capacity.[16,17] Side effects potentially related to ropivacaine and bupivacaine were also recorded.

Statistical Analysis

This randomized superiority study was designed to have 90% power to detect a between-group difference in within-patient PVR difference (Δ) of 180 ml during TEA postoperatively *versus* before TEA using a two-sided *t* test at a significance level of 5%, assuming a SD of 210 ml.[6,7] Such a difference is considered clinically relevant.[18] This resulted in a sample size of 17 patients/group. Assuming a drop out of around 20%, 42 patients (*i.e.*, 21 patients in the bupivacaine group and 21 in the ropivacaine group) were enrolled.

Statistical analyses were conducted on a modified intention-to-treat basis because patients who did not have the second urodynamic investigation had to be excluded from the analysis. The data are expressed in medians with ranges for continuous variables or frequencies for categorical ones. For quantitative endpoints, the two groups were compared using the Wilcoxon rank-sum test, accompanied with point estimate and 95% CIs for Hodges–Lehmann estimator for differences of the two group medians for each of the pairwise comparisons. Within each group, the within-patient prepostoperative differences were analyzed using the Wilcoxon signed-rank test. Categorical endpoints were analyzed using the Fisher's exact test. A two-sided *P* value of less than 0.05 was considered statistically significant. The statistical software used was IBM SPSS Statistics 24.0 (SPSS Inc., USA).

Results

Between April 2015 and May 2017, a total of 62 patients were assessed for eligibility, and 42 patients underwent randomization. Two patients in the bupivacaine group (TEA with insufficient segmental blockade (n = 1) and refusal to undergo the second urodynamic investigation during TEA (n = 1) and 4 patients in the ropivacaine group (TEA with insufficient segmental blockade (n = 1) and refusal to undergo the second urodynamic investigation during TEA (n = 3) dropped out (fig. 2). Baseline characteristics and pain scores were similar between the two groups (table 1). The upper and lower segmental level of analgesia did not differ significantly between the groups. No systemic opioids and no sedatives were administrated postoperatively, and no postoperative nausea and vomiting were documented. No motor blockade related to TEA was present (Bromage motor block score of 0 in all patients). No adverse events related to the drugs administered occurred.

Voiding Phase

Within-patients differences in voiding phase parameters were all statistically significant (table 2). Median ΔPVR from baseline to postoperatively was 300 ml (range 30 to 510; $P < 0.001$) in the bupivacaine group and 125 ml (range, –30 to 350; $P = 0.011$) in the ropivacaine group; with a significant difference between the groups (Hodges–Lehmann median difference, –175; 95% CI –295 to –40; $P = 0.012$; fig. 3). Median Δ voided volume was –320 ml (range, –800 to –50; $P < 0.001$) in the bupivacaine group and –70 ml (range, –600 to 0; $P = 0.005$) in the ropivacaine group, with a significant difference between the groups (Hodges–Lehmann median difference, 250; 95% CI, 50 to 375; $P = 0.003$). Median Δ maximum flow rate was significantly more pronounced in the bupivacaine group (–12 ml/s; range, –28 to 3; $P < 0.001$) than in the ropivacaine group (–4 ml/s; range, –16 to 7; $P = 0.025$), and this difference was significant between the groups (Hodges–Lehmann median difference, 7; 95% CI, 0 to 12; $P = 0.028$). Four patients (2 women and 2 men) in the bupivacaine group (21%) and 2 patients (2 men) in the ropivacaine group (12%) had a maximum flow rate of 0 ml/s during TEA postoperatively and were totally unable to void ($P = 0.664$).

The bladder contractility index was significantly reduced in both groups: bupivacaine group (–59; range, –140 to 17;

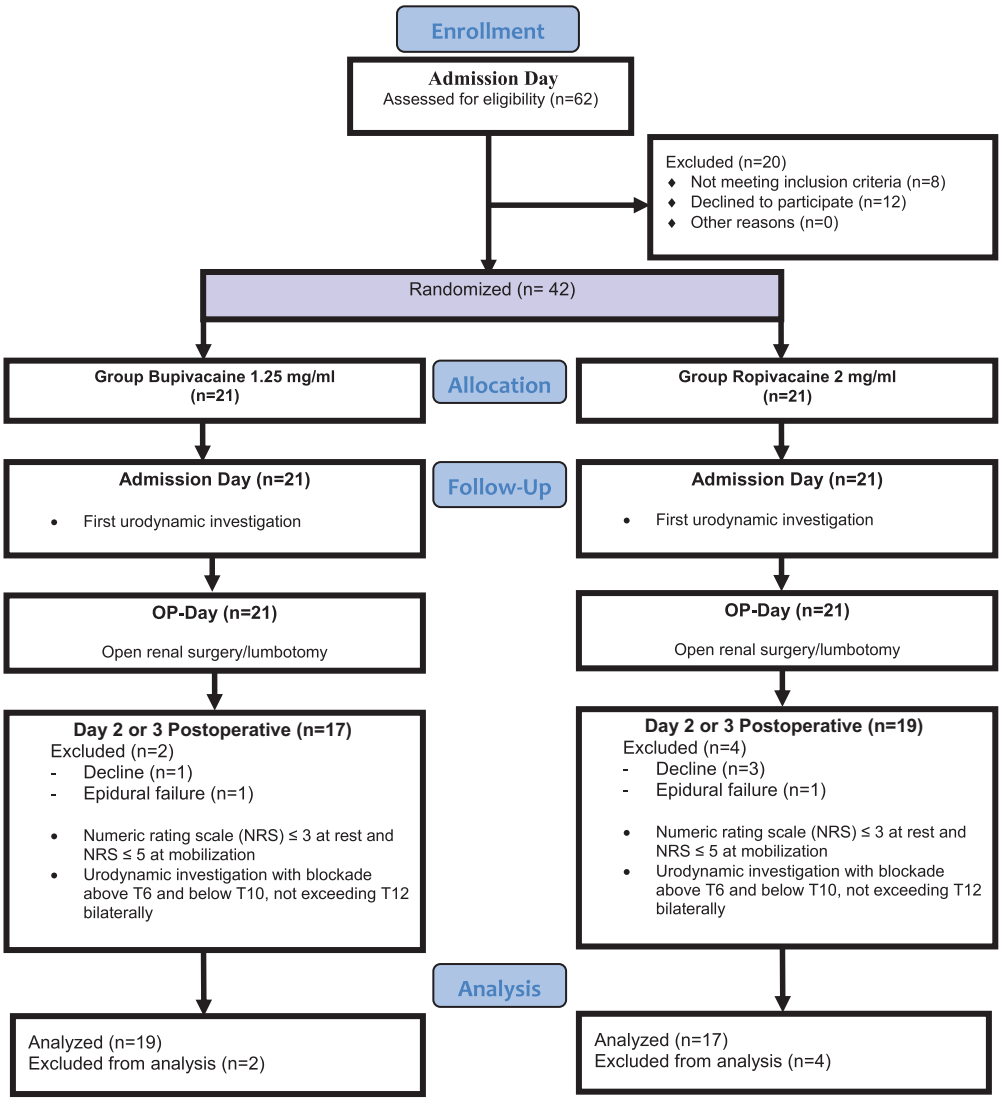

Fig. 2. Consolidated Standards of Reporting Trials flow diagram indicating the urodynamic protocols in the study groups. NRS = numerical rating scale.

Table 1. Baseline Characteristics

	Bupivacaine Group (n = 19)	Ropivacaine Group (n = 17)	*P* Value	Estimate of Group Difference	95% CI
Sex (women/men)	6/13	8/9	0.342		
ASA classification (II/III)	10/9	8/9	0.739		
Age (yr)	59 (43, 77)	55 (27, 70)	0.999	–4	–14 to 3
IPSS	2 (0, 7)	3 (1, 6)	0.235	1	0 to 2
IPSS QoL (1/2/3)	10/9/0	7/7/3	0.159		
Epidural mixture rate postoperatively (ml/h)	8 (4, 12)	8 (4, 12)	0.334	–1	–2 to 1
NRS at rest	0 (0, 3)	0 (0, 3)	0.650	0	0 to 0
NRS during mobilization	2 (1, 5)	2 (1, 5)	0.524	0	–1 to 0
Segmental blockade					
Upper thoracic dermatome	4 (3, 6)	4 (4, 6)	0.986	0	0 to 0
Lower thoracic dermatome	12 (11, 12)	12 (10, 12)	0.899	0	0 to 0

The data are presented as count or median value (range).

ASA = American Society of Anesthesiologists; CI = confidence interval; IPSS = international prostate symptom score; QoL = quality of life; NRS = numeric rating scale for pain, in which 0 = no pain and 10 = worst pain imaginable.

Table 2. Within-patient Absolute Values and Difference (Value during TEA – Baseline Value) and Between-group Estimate of Difference (Ropivacaine Group *vs*. Bupivacaine Group) of the Parameters of the Voiding Phase

	Median (Range)		Ropivacaine *vs.* Bupivacaine Group	
	Bupivacaine Group (n = 19)	Ropivacaine Group (n = 17)	Estimates (95% CI)	*P* Value*
Postvoid residual (ml)			–175 (–295 to –40)	0.012
Baseline	10 (0 to 70)	25 (0 to 95)		
During TEA	325 (50 to 700)	125 (0 to 350)		
Within-patient difference	300 (30 to 510)	125 (–30 to 350)		
P value†	< 0.001	0.011		
Voided volume (ml)			250 (50 to 375)	0.003
Baseline	520 (150 to 960)	350 (210 to 600)		
During TEA	125 (0 to 745)	300 (0 to 535)		
Within-patient difference	–320 (–800 to -50)	–70 (–600 to 0)		
P value†	< 0.001	0.005		
Maximum detrusor pressure (cmH_2O)			4 (–8 to 12)	0.842
Baseline	33 (1 to 80)	35 (10 to 75)		
During TEA	23 (0 to 80)	29 (0 to 74)		
Within-patient difference	–7 (–35 to 50)	–3 (–52 to 1)		
P value†	0.017	0.003		
Detrusor pressure at maximum flow rate (cmH_2O)			7 (–5 to 19)	0.250
Baseline	28 (8 to 60)	34 (8 to 61)		
During TEA	15 (0 to 62)	25 (0 to 60)		
Within-patient difference	–12 (–31 to 7)	–5 (–46 to 8)		
P value†	0.001	0.013		
Maximum flow rate (ml/s)			7 (0 to 12)	0.028
Baseline	18 (11 to 42)	16 (9 to 20)		
During TEA	6 (0 to 27)	11 (0 to 27)		
Within-patient difference	–12 (–28 to 3)	–4 (–16 to 7)		
P value†	< 0.001	0.025		
Bladder contractility index			31 (4 to 59)	0.022
Baseline	125 (91 to 228)	114 (87 to 132)		
During TEA	48 (0 to 150)	80 (0 to 154)		
Within-patient difference	–59 (–140 to 17)	–28 (–114 to 26)		
P value†	< 0.001	0.002		
Bladder voiding efficiency (%)			42 (4 to 71)	0.016
Baseline	97 (65 to 174)	95 (60 to100)		
During TEA	27 (0 to 100)	85 (0 to 103)		
Within-patient difference	–53 (–100 to 3)	–10 (–100 to 9)		
P value†	< 0.001	0.124		

*Within-group *P* value derived from the Wilcoxon signed rank test for within-patient value during TEA – baseline value difference of each endpoint. †Between-group *P* value from Wilcoxon rank sum test for within-patient value during TEA – baseline value difference. Point estimates for Hodges–Lehmann median difference with 95% CI were constructed accordingly. Two-sided *P* value < 0.05 as statistically significant.

CI = confidence interval; TEA = thoracic epidural analgesia.

P < 0.001) ropivacaine group (–28; range, –114 to 26; *P* = 0.002), and this difference was significant between the groups (Hodges–Lehmann median difference, 31; 95% CI, 4 to 59; *P* = 0.022). Bladder voiding efficiency was significantly reduced in the bupivacaine group (–53%; range, –100 to 3; *P* < 0.001) but not in the ropivacaine group (–10%; range, –100 to 9; *P* = 0.124); this difference was significant between the groups (Hodges–Lehmann median difference 42; 95% CI, 4 to 71; *P* = 0.016).

Storage Phase

Between-group differences in storage phase parameters did not differ significantly (table 3). Within-patient median Δ bladder compliance was –46 ml/cmH_2O (range, –473 to 45; *P* < 0.001) in the bupivacaine group. No adverse events (urinary tract infections, pain in the urinary tract requiring analgesic treatment) related to the urodynamic investigations occurred.

Discussion

TEA with ropivacaine has a less pronounced effect on voiding function than with bupivacaine. Although segmental blockade from around T4 to T12 with both drugs was associated with a relevant impairment in voiding function, patients in the bupivacaine group developed clinically relevant PVRs. The median ΔPVR of at least 200 ml during TEA in the bupivacaine group represents a clinically relevant impairment in voiding function, which is associated with an

increased risk of complications (urinary tract infection).[19] In addition, 21% of the patients in the bupivacaine group and 12% in the ropivacaine group were completely unable to void (*i.e.*, urine flow rate of 0), even though we could not detect a statistical significance; this finding is clinically relevant because these patients need catheterization.

Our results confirm our previous observation that segmental blockade with epidurally administered local anesthetics results in detrusor underactivity and a decreased flow rate.[8] However, the administration of ropivacaine resulted in less dramatic reduction of urinary flow rate, explaining the lower ΔPVR and higher voided volume differences compared to bupivacaine. The differences in bladder contractility index reflecting the strength of detrusor contraction and bladder voiding efficiency were larger in the bupivacaine group, reflecting the greater impact on the detrusor muscle also significantly reduced in the bupivacaine group compared to the ropivacaine group.

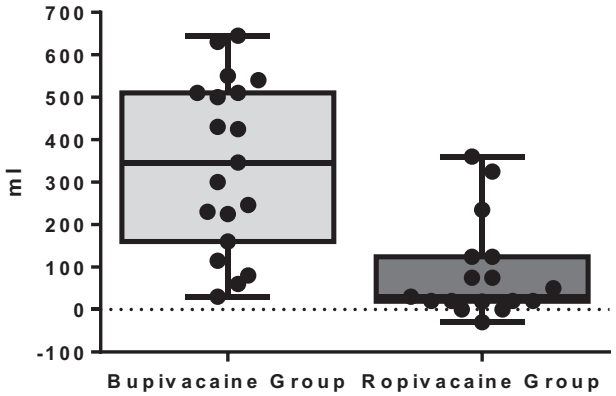

Fig. 3. Differences in postvoid residual urine volume shown as median with interquartile ranges and with maximum and minimum values ($P = 0.012$).

Bupivacaine and ropivacaine have nearly identical chemical structure; the only difference is a propyl group and a butyl group attached to the pipechol ring for ropivacaine and bupivacaine, respectively, making ropivacaine a smaller molecule than bupivacaine.[10] The analgesic potency of ropivacaine is around 60% of that of bupivacaine. For this reason, to achieve an equipotent effect, bupivacaine 0.125% was compared with ropivacaine 0.2%, and we did find similar pain scores at rest and during mobilization in the two groups. Ropivacaine, however, produced a greater dissociation of sensory to motor block than bupivacaine. This is in line with the fact that in terms of motor block, ropivacaine is 66% less potent than bupivacaine.[20,21] In addition, there is a minimal advantage in terms of toxicity in favor of ropivacaine. The reduced effect of ropivacaine on detrusor contractility could be explained by a decreased affinity for sodium channels in motor neurons. Different affinities for various subtypes of sodium channels have been demonstrated in other studies,

Table 3. Within-patient Absolute Values and Difference (Value during TEA – Baseline Value) and Between-group Estimate of Difference (Ropivacaine Group *vs*. Bupivacaine Group) of the Parameters of the Storage Phase

	Median (Range)		Ropivacaine *vs.* Bupivacaine Group	
	Bupivacaine Group (n = 19)	Ropivacaine Group (n = 17)	Estimate (95% CI)	*P* Value*
Bladder volume at first desire to void (ml)			13 (–61 to 55)	0.730
Baseline	260 (30 to 470)	180 (80 to 355)		
During TEA	220 (50 to 610)	200 (60 to 400)		
Within-patient difference	–8 (–120 to 195)	5 (–100 to 320)		
P value†	0.825	0.649		
Bladder volume at strong desire to void (ml)			45 (–25 to 123)	0.128
Baseline	460 (140 to 815)	305 (160 to 625)		
During TEA	385 (100 to 700)	310 (85 to 500)		
Within-patient difference	–50 (–315 to 160)	–5 (–165 to140)		
P value†	0.021	0.415		
Maximum cystometric capacity (ml)			–28 (–100 to 70)	0.413
Baseline	545 (200 to 970)	420 (210 to 625)		
During TEA	460 (140 to 745)	350 (140 to 540)		
Within-patient difference	–14 (–420 to 245)	–41 (–190 to 10)		
P value†	0.287	0.003		
Compliance (ml/cmH_2O)			35 (–8 to 72)	0.842
Baseline	89 (17 to 500)	50 (19 to 100)		
During TEA	36 (13 to 240)	35 (17 to 400)		
Within-patient difference	–46 (–473 to 45)	–10 (–100 to 25)		
P value†	< 0.001	0.109		

*Between-group *P* value from Wilcoxon rank sum test for within-patient value during TEA – baseline value difference. Point estimates for Hodges–Lehmann median difference with 95% CI were constructed accordingly. Two-sided *P* value < 0.05 as statistically significant. †Within-group *P* value derived from the Wilcoxon signed rank test for within-patient value during TEA – baseline value difference of each endpoint.

CI = confidence interval; TEA = thoracic epidural analgesia.

e.g., the subtype Na(v)1.8.[22] It is unclear, however, how this applies to ropivacaine. In addition, ropivacaine is less lipophilic than bupivacaine. The decreased lipophilicity reduces the penetration of the larger myelinated nerve fibers (Aα, Aβ, and Aδ fibers) by ropivacaine due to the substitution of the pipecoloxylidine with a three-carbon side chain instead of a four-carbon side chain.[23,24] In a similar way, the less lipophilic properties of ropivacaine could result in smaller amounts of local anesthetic penetrating the dura mater, which would further explain the decreased potency and smaller degree of motor block.[25] This remains speculative because these are *in vitro* observations and with higher concentrations than used in this study.[26–28] The different physiochemical properties of the two local anesthetics may also play a role because ropivacaine is an almost pure L-isomer, and bupivacaine is a racemic mixture; the D-isomer of bupivacaine could alter receptor binding in larger nerve fibers.[9]

Another issue is the nature of the epidural space and the distribution of local anesthetics, demonstrated in a cadaver study using cryomicrotome sections. Hogan *et al.*[29] found that the distribution of drugs injected in the epidural space follows paths between structures according to pressures by which they are compressed. This could explain the wide CIs and why some patients in both groups were able to void with unchanged voided volumes and PVRs while others had bladder retention with detrusor undercontractility.

Bupivacaine also had a greater effect on bladder compliance than ropivacaine, however, without fulfilling the criteria of a low compliant bladder.[30] This observation is similar to our precedent studies involving epidurally administered bupivacaine 0.125% with or without additional fentanyl. On the other hand, maximum cystometric capacity was significantly reduced in the ropivacaine group. This may explain the more effective voiding because the less-filled bladder may contract more effectively according to the law of Laplace.

Early catheter removal after surgery in an attempt to avoid or minimize the rate of urinary tract infections and urethral trauma has become a major focus of interest and is part of enhanced recovery programs.[31–33] Despite the reduced effect of ropivacaine on bladder function, proper assessment and monitoring of PVRs during TEA is still recommended because some patients were unable to void. Because patients report a sensation of bladder filling even when the bladder is not filled, an objective quantification is mandatory even in case if sensory function should be considered as intact.[34]

We are aware of certain limitations of our study: silent voiding dysfunction may be unmasked during TEA or after surgery, and our study was not placebo-controlled; however, placebo TEA for postoperative analgesia would give rise to ethical concerns. In this study, we considered a PVR of more than 200 ml clinically relevant in patients with normal preoperative voiding function; however, this value has been challenged. Brouwer *et al.*[35] found that using an individual residual volume based on maximum cystometric capacity rather than a fixed volume could lead to a decrease in catheterization.

In conclusion, thoracic epidurally administrated bupivacaine 0.125% led to a more pronounced impairment of detrusor activity with a greater increase in PVRs than ropivacaine 0.2%. Based on our results, ropivacaine 0.2% is the preferred drug to achieve early catheter removal. However, because detrusor contractility is also affected with ropivacaine 0.2%, careful monitoring of PVRs remains recommended.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: patrick.wuethrich@insel.ch. Raw data available at: patrick.wuethrich@insel.ch.

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References

1. Baldini G, Bagry H, Aprikian A, Carli F: Postoperative urinary retention: Anesthetic and perioperative considerations. ANESTHESIOLOGY 2009; 110:1139–57
2. Givens CD, Wenzel RP: Catheter-associated urinary tract infections in surgical patients: A controlled study on the excess morbidity and costs. J Urol 1980; 124:646–8
3. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, Cardo DM: Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007; 122:160–6
4. Foxman B: Epidemiology of urinary tract infections: Incidence, morbidity, and economic costs. Am J Med 2002; 113(suppl 1A):5S–13S
5. Rosseland LA, Stubhaug A, Breivik H, Medby PC, Larsen HH: [Postoperative urinary retention]. Tidsskr Nor Laegeforen 2002; 122:902–4
6. Wuethrich PY, Burkhard FC, Panicker JN, Kessler TM: Effects of thoracic epidural analgesia on lower urinary tract function in women. Neurourol Urodyn 2011; 30:121–5
7. Wuethrich PY, Kessler TM, Panicker JN, Curatolo M, Burkhard FC: Detrusor activity is impaired during thoracic epidural analgesia after open renal surgery. ANESTHESIOLOGY 2010; 112:1345–9
8. Wuethrich PY, Metzger T, Mordasini L, Kessler TM, Curatolo M, Burkhard FC: Influence of epidural mixture and surgery

on bladder function after open renal surgery: A randomized clinical trial. Anesthesiology 2013; 118:70–7

9. Meister GC, D'Angelo R, Owen M, Nelson KE, Gaver R: A comparison of epidural analgesia with 0.125% ropivacaine with fentanyl *versus* 0.125% bupivacaine with fentanyl during labor. Anesth Analg 2000; 90:632–7
10. Beilin Y, Halpern S: Focused review: Ropivacaine *versus* bupivacaine for epidural labor analgesia. Anesth Analg 2010; 111:482–7
11. Madersbacher S, Pycha A, Klingler CH, Schatzl G, Marberger M: The International Prostate Symptom score in both sexes: A urodynamics-based comparison. Neurourol Urodyn 1999; 18:173–82
12. Hampson SJ, Noble JG, Rickards D, Milroy EJ: Does residual urine predispose to urinary tract infection? Br J Urol 1992; 70:506–8
13. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, Sterling AM, Zinner NR, van Kerrebroeck P; International Continence Society: Good urodynamic practices: Uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002; 21:261–74
14. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A; Standardisation Sub-committee of the International Continence Society: The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21:167–78
15. Curatolo M, Petersen-Felix S, Arendt-Nielsen L: Sensory assessment of regional analgesia in humans: A review of methods and applications. Anesthesiology 2000; 93:1517–30
16. Abrams P: Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: Three simple indices to define bladder voiding function. BJU Int 1999; 84:14–5
17. Osman NI, Chapple CR, Abrams P, Dmochowski R, Haab F, Nitti V, Koelbl H, van Kerrebroeck P, Wein AJ: Detrusor underactivity and the underactive bladder: a new clinical entity?: A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. Eur Urol 2014; 65:389–98
18. Panicker JN, Fowler CJ: The bare essentials: uro-neurology. Pract Neurol 2010; 10:178–85
19. Truzzi JC, Almeida FM, Nunes EC, Sadi MV: Residual urinary volume and urinary tract infection: When are they linked? J Urol 2008; 180:182–5
20. Lacassie HJ, Columb MO, Lacassie HP, Lantadilla RA: The relative motor blocking potencies of epidural bupivacaine and ropivacaine in labor. Anesth Analg 2002; 95:204–8
21. Lacassie HJ, Habib AS, Lacassie HP, Columb MO: Motor blocking minimum local anesthetic concentrations of bupivacaine, levobupivacaine, and ropivacaine in labor. Reg Anesth Pain Med 2007; 32:323–9
22. Ekberg J, Jayamanne A, Vaughan CW, Aslan S, Thomas L, Mould J, Drinkwater R, Baker MD, Abrahamsen B, Wood JN, Adams DJ, Christie MJ, Lewis RJ: muO-conotoxin MrVIB selectively blocks Nav1.8 sensory neuron specific sodium channels and chronic pain behavior without motor deficits. Proc Natl Acad Sci U S A 2006; 103:17030–5
23. Casati A, Putzu M: Bupivacaine, levobupivacaine and ropivacaine: Are they clinically different? Best Pract Res Clin Anaesthesiol 2005; 19:247–68
24. Kuthiala G, Chaudhary G: Ropivacaine: A review of its pharmacology and clinical use. Indian J Anaesth 2011; 55:104–10
25. Higuchi H, Adachi Y, Kazama T: Factors affecting the spread and duration of epidural anesthesia with ropivacaine. Anesthesiology 2004; 101:451–60
26. Bader AM, Datta S, Flanagan H, Covino BG: Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 1989; 68:724–7
27. Feldman HS, Covino BG: Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Anesth Analg 1988; 67:1047–52
28. Zaric D, Nydahl PA, Philipson L, Samuelsson L, Heierson A, Axelsson K: The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: A double-blind study. Reg Anesth 1996; 21:14–25
29. Hogan Q: Distribution of solution in the epidural space: Examination by cryomicrotome section. Reg Anesth Pain Med 2002; 27:150–6
30. Cho SY, Yi JS, Oh SJ: The clinical significance of poor bladder compliance. Neurourol Urodyn 2009; 28:1010–4
31. Basse L, Werner M, Kehlet H: Is urinary drainage necessary during continuous epidural analgesia after colonic resection? Reg Anesth Pain Med 2000; 25:498–501
32. Zaouter C, Kaneva P, Carli F: Less urinary tract infection by earlier removal of bladder catheter in surgical patients receiving thoracic epidural analgesia. Reg Anesth Pain Med 2009; 34:542–8
33. Leuck AM, Wright D, Ellingson L, Kraemer L, Kuskowski MA, Johnson JR: Complications of Foley catheters: Is infection the greatest risk? J Urol 2012; 187:1662–6
34. De Wachter S, Van Meel TD, Wyndaele JJ: Can a faked cystometry deceive patients in their perception of filling sensations?: A study on the reliability of spontaneously reported cystometric filling sensations in patients with non-neurogenic lower urinary tract dysfunction. Neurourol Urodyn 2008; 27:395–8
35. Brouwer TA, Rosier PF, Moons KG, Zuithoff NP, van Roon EN, Kalkman CJ: Postoperative bladder catheterization based on individual bladder capacity: A randomized trial. Anesthesiology 2015; 122:46–54