

## Intrathecal use of ropivacaine : a review

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**Summary :** Spinal anesthesia is a very old and popular anesthetic technique, with a high success rate and a good safety profile. In order to further improve and understand safety issues as well as the clinical use of spinal anesthesia, new local anesthetics and analgesic additives are being investigated for different applications. As practice of medicine focuses increasingly on outpatient care, spinal anesthetics should provide short-acting and adequate anesthesia without compromising early ambulation and discharge from the day surgery unit. A review of the current literature suggests that ropivacaine could have potential in this area.

### INTRODUCTION

Ropivacaine was introduced into clinical practice in 1996, and has consistently demonstrated an improved safety profile over bupivacaine, with a reduced CNS and cardiotoxic potential, together with a wide clinical utility at different doses and for a wide range of indications. It has been shown to provide effective, well tolerated surgical anesthesia via the epidural route, for major and minor nerve blocks and field blocks as well as high-quality postoperative analgesia.

Ropivacaine is a long-acting, enantiomerically pure (S-enantiomer) amide local anesthetic, with a low lipid solubility which blocks nerve fibers involved in pain transmission (A $\delta$  and C fibres) to a greater degree than those controlling motor function (A $\beta$  fibres).

Ropivacaine was approved for a new route of administration, the intrathecal route, in the European Union in February 2004.

Spinal or intrathecal anesthesia has a long history of success and has recently become more popular, mostly due to an increasing number of ambulatory procedures and interventions, for which the ideal spinal anesthetic would provide rapid and adequate surgical anesthesia together with early ambulation and ability to void to allow early discharge.

Reports of transient radicular irritation (TRI) after lidocaine spinal anesthesia prompted the search for alternatives and ropivacaine could be promising in this setting.

### DOSE-FINDING STUDIES

Clinical experience with ropivacaine for intrathecal use includes dose-finding studies. These have shown that spinal ropivacaine is effective and well-tolerated for several indications.

In the studies from VAN KLEEF *et al.*(1) and WAHEDI *et al.*(2), patients were scheduled for orthopedic, gynecological and urological surgery and were randomized to receive either 3 ml of plain (isobaric) ropivacaine of either 5 mg/ml or 7.5 mg/ml (15 or 22.5 mg).

These studies concluded that for gynecological, urological and minor orthopedic surgery, the spread of anesthesia was variable (1), the duration of analgesia and motor block were longer in the 22.5 mg group and the intensity of motor block was lower in the 15 mg group (1, 2).

Two other double-blind randomized studies described the use of intrathecal ropivacaine in patients scheduled for total hip arthroplasty (3, 4). In the first study, patients received 2.5 ml of a plain isolution of ropivacaine of either 7.5 mg/ml or 10 mg/ml (18.75 mg or 25 mg). In the second study, 3.5 ml of plain ropivacaine 5 mg/ml or 3.5 ml of plain bupivacaine 5 mg/ml were compared.

MCNAMEE *et al.* (3) demonstrated a lower degree of motor block with 7.5 mg/ml compared to 10 mg/ml, and McCLELLAND *et al.* (4) showed that 17.5 mg ropivacaine (5 mg/ml) produced a similar efficacy and tolerability profile compared with bupivacaine 17.5 mg, although there was a shorter duration of sensory and motor block after ropivacaine administration.

No neurotoxic effects were observed in any of these studies.

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## INTRATHECAL ROPIVACAINE FOR ORTHOPEDIC SURGERY

The efficacy and tolerability of ropivacaine for spinal anesthesia in orthopedic surgery have been demonstrated in several studies.

*Ropivacaine versus bupivacaine for orthopedic surgery*

GAUTIER *et al.* (5) published on the use of intrathecal ropivacaine or bupivacaine for ambulatory knee arthroscopy. They found that ropivacaine 12 mg produced a sensor and motor block almost comparable to the block with bupivacaine 8 mg. Lower doses of ropivacaine (8 or 10 mg) produced significantly lower quality of intraoperative analgesia, as assessed by the patient. Higher doses of ropivacaine (14 mg) significantly increased the time to void, while sensor and motor block were comparable to the 12 mg group. No signs of transient radicular irritation (TRI) were noted.

When isobaric ropivacaine 0.5% was compared to bupivacaine 0.5% by DELFINO *et al.*(6), there were no significant differences regarding the upper sensory block level or the time to achieve it. However, the time of onset of non-stimulated pain at the surgical site and the duration of motor block were significantly shorter in the ropivacaine group. As a conclusion, when compared to bupivacaine at the same dose, spinal ropivacaine 15 mg (5 mg/ml) allowed for good analgesia and motor block for surgical purposes.

Another study in orthopedic surgery (total hip arthroplasty) compared 17.5 mg of intrathecal ropivacaine (5 mg/ml) with the same dose of bupivacaine (7). Onset of sensor and motor block were rapid, with no significant differences between the two groups. Recovery of sensor and motor block were more rapid with ropivacaine.

*Ropivacaine versus levobupivacaine for orthopedic surgery*

DELFINO *et al.*(8) compared 15 mg of spinal ropivacaine with the same dose of levobupivacaine for lower limb surgery. There were no significant differences in the most variables observed. However, the time for onset of non-stimulated pain at the surgical site and the time for reversal of total motor block were significantly longer in the levobupivacaine group. The authors concluded that both 15 mg of ropivacaine and levobupivacaine provided adequate analgesia and motor blockade for lower limb surgery.

In a study from BREEBAART *et al.*(9), the intrathecal use of 15 mg of ropivacaine, 10 mg of levobupivacaine and 60 mg of lidocaine were compared for day-case arthroscopy. All 3 comparators provided similar quality of sensory and motor block, but lidocaine allowed a slightly shorter, but not clinically significant, time to voiding and discharge.

*Additives to intrathecal ropivacaine for orthopedic surgery*

In order to maintain the advantage of low-dose ropivacaine while improving intraoperative quality of anesthesia, the use of analgesic adjuvants has been proven to be very valuable.

This was studied by DE KOCK *et al.*(10) in a dose-response study, investigating the effects of adding clonidine (15, 45 or 75 µg) to a fixed dose of isobaric, spinal ropivacaine (8 mg) for ambulatory knee arthroscopy.

The addition of a small dose (15 µg) of intrathecal clonidine to a small dose of ropivacaine produced adequate and short-lasting anesthesia for knee arthroscopy. There was a significant improvement of the subjective parameters that reflect the quality of intraoperative analgesia, this without compromising benefits as early mobilization (short lasting motor block) or early voiding.

Other studies have demonstrated that the quality of analgesia with low dose ropivacaine can be improved by adding opioids (11). In one study, 40 patients scheduled for knee arthroscopy were randomized to receive either intrathecal ropivacaine 1% (10 mg) + fentanyl 25 µg + 1.5 ml isotonic NaCl or intrathecal bupivacaine 0.5% (10 mg) + fentanyl 25 µg + 0.5 ml isotonic NaCl. The results showed that onset time for motor blockade was shorter but that the duration of motor blockade was longer in the bupivacaine group. Offset time of sensory block to L1, first ambulation and first voiding were longer in the bupivacaine group. The authors concluded that low dose of ropivacaine with fentanyl had a shorter duration of motor and sensor block, and also a shorter time to ambulation and voiding. Interesting is that also discharge times were shorter in ropivacaine group.

Another study looked at the use of intrathecal ropivacaine with or without fentanyl for arthroscopy of the knee (12). Patients were randomized to receive either isobaric ropivacaine 0.75% (2 ml) + 1 ml isotonic NaCl or isobaric ropivacaine 1% (1 ml) + 25 µg fentanyl + 1.5 ml isotonic NaCl in the lateral decubitus position.

There was no statistical difference in onset time for motor blockade, onset time for sensory blockade to T10, total motor block, first ambulation or first voiding and discharge time. The duration of the sensor and motor block was shorter in the group with fentanyl and there was a higher cephalad spread in the group without fentanyl.

The authors concluded that the addition of 25 µg of fentanyl to a low dose (10 mg) of ropivacaine for intrathecal anesthesia provided a shorter motor and sensor block than the use of ropivacaine (15 mg) alone.

#### INTRATHECAL ROPIVACAINE FOR CESAREAN SECTION

Several studies have demonstrated the efficacy and tolerability of spinal anesthesia with ropivacaine for C-section.

##### *Dose-finding studies for cesarean section*

In a dose-finding, double-blind randomized study from KHAW *et al.* in 2001 (13), different doses (10, 15, 20 and 25 mg) of ropivacaine were evaluated (after dilution to a total volume of 3 ml with normal saline). A dose was considered effective if an upper sensory level to pin prick of T7 or above was achieved and epidural supplementation was not required intraoperatively.

Adequacy of spinal anesthesia was related to dose and to the degree of motor block, but was poorly correlated with upper level of sensory changes.

The effective dose (ED<sub>50</sub> and ED<sub>95</sub>) for spinal ropivacaine was calculated to be 16.7 mg (ED<sub>50</sub>) and 26.8 mg (ED<sub>95</sub>). The ED<sub>95</sub> was above the actually tested dose, but was obtained by extrapolation.

##### *Plain versus hyperbaric ropivacaine for cesarean section*

Isobaric (plain) spinal ropivacaine (25 mg in saline) and hyperbaric solutions (25 mg in glucose 8.3%) of ropivacaine were compared for C-section by KHAW *et al.* in 2002 (14). The aim of this double-blind, randomized trial was to test the hypothesis that by increasing the baricity of the local anesthetic (by addition of glucose), the clinical characteristics of the subarachnoid block would change.

Hyperbaric ropivacaine produced spinal anesthesia with a higher success rate which was reflected in a faster onset and offset of motor and sensor

block, with a higher cephalad spread and a lower coefficient of variation of maximum block height. No neurological symptoms were noted after 24 h.

It should be noted that there is no hyperbaric formulation of ropivacaine approved or commercially available.

##### *Hyperbaric ropivacaine versus hyperbaric bupivacaine for cesarean section*

Hyperbaric spinal ropivacaine 18 mg (5 mg/ml) was compared to hyperbaric bupivacaine 12 mg (5 mg/ml) for C-section by Chung *et al.* (15). The purpose of this study was to evaluate the efficacy and safety of spinal anesthesia with 0.5% hyperbaric ropivacaine versus 0.5% hyperbaric bupivacaine.

The hyperbaric solution of ropivacaine was prepared with 4 ml ropivacaine 7.5 mg/ml + 2 ml of 20% dextrose. The hyperbaric bupivacaine solution comprised 12 mg (5 mg/ml) bupivacaine in 8% glucose.

18 mg of 0.5% hyperbaric ropivacaine provided effective and similar spinal anesthesia with a later onset of sensory block and a shorter duration of sensor and motor block, compared with 12 mg of 0.5% hyperbaric bupivacaine for C-section. The intraoperative quality of anesthesia was excellent in both groups and there was no difference in side effects.

##### *Adjuvants to intrathecal ropivacaine for cesarean section*

###### *∞ Ropivacaine versus bupivacaine with morphine*

Intrathecal isobaric ropivacaine (15 mg)-morphine (150 µg) versus isobaric bupivacaine (15 mg)-morphine (150 µg) were studied by ÖGÜN *et al.* (16).

Both treatment provided effective sensor and motor block, but the ropivacaine-morphine group resulted in a shorter motor block. And although the bupivacaine-morphine group required more ephedrine than the ropivacaine-morphine group, the number of patients requiring ephedrine was similar and the APGAR scores and umbilical blood pH values of the neonates were within the normal ranges.

In a similar study from DANELLI *et al.* (17), 20 mg of plain ropivacaine was compared to 15 mg of plain bupivacaine, both supplemented with morphine 0.1 mg. The aim of the study was to compare clinical efficacy and safety of both local anesthetics for intrathecal use in C-section.

Both solutions produced effective and safe anesthesia, but with a faster recovery of sensor and motor block in the ropivacaine group.

Unexpectedly, a higher incidence of itching was observed in patients receiving bupivacaine than those treated with ropivacaine. The authors speculated that the vasoconstrictive properties of ropivacaine could play a role in this phenomenon.

No signs of TNS were reported up to 1 week after surgery.

#### ∞ *Ropivacaine versus levobupivacaine or bupivacaine with sufentanil*

GAUTIER *et al.* (18) compared 12 mg of ropivacaine with 8 mg of levobupivacaine or bupivacaine, all combined with sufentanil 2.5 µg. The solution was considered effective if an upper sensory level to pin-prick of T4 or above was achieved and if intraoperative epidural supplementation was not required.

The addition of sufentanil 2.5 µg allowed a reduction of nearly 50% of the dose of ropivacaine required for the ED<sub>90</sub>, which was calculated to be 24.5 mg in the dose-finding study by KHAW *et al.* (13) published in 2001.

#### *Motor blocking potencies of intrathecal ropivacaine for cesarean section : effects on concentration*

In a recent prospective, double-blind, randomised, sequential allocation study, CAMORCIA *et al.* (19) wanted to estimate the ED<sub>50</sub> for motor blocking potencies for two concentrations of intrathecal ropivacaine (1% and 0.1%), and then tried to determine the effects of concentration on dose requirements for motor block. All included parturients underwent C-section with a combined spinal-epidural technique (CSE). The initial dose was chosen to be 4 mg, with subsequent doses being determined by the response of the previous patient (testing interval of 1 mg). Occurrence of any motor block in either lower limb within 5 minutes from the intrathecal injection of the study solution was considered effective.

The minimum local anesthetic dose for motor block of 0.1% ropivacaine was 50% larger than 1% ropivacaine, with a relative efficacy ratio of 1.5. The authors conclude that these results should encourage further investigations to study the appropriate concentration of local anesthetics for ambulant CSE analgesia, suggesting that more diluted local anesthetics cause less motor block.

#### INTRATHECAL ROPIVACAINE IN ABDOMINAL GYNECOLOGICAL SURGERY

In a study by KESSLER *et al.* (20), 60 patients (scheduled for lower abdominal gynecological surgery) were randomized to receive intrathecal ropivacaine 0.75% (22.5 mg) or intrathecal bupivacaine 0.5% (15 mg).

Bromage grade III was achieved in 94% of the patients in the ropivacaine group and in 97% of the patients in the bupivacaine group. A greater sensory spread was noted in the bupivacaine group (Th 8 versus Th 9.7).

The authors concluded that isobaric ropivacaine (22.5 mg) was suitable for spinal anesthesia for this type of surgery.

#### INTRATHECAL ROPIVACAINE IN UROLOGICAL SURGERY

Limited data have been published on the intrathecal use of ropivacaine for urological surgery. MALINOVSKY *et al.* (21) compared isobaric ropivacaine (15 mg) and isobaric bupivacaine (10 mg) for this type of surgery.

The cephalad spread of anesthesia was higher in the bupivacaine group. Onset and offset time and intensity of motor block were similar in both groups. The authors concluded that ropivacaine is less potent than bupivacaine, and that ropivacaine is ineffective for endoscopic procedures of the lower urological tract.

Intrathecal hyperbaric ropivacaine (10 mg in a volume of 4 ml) was compared to the same dose and volume of hyperbaric bupivacaine for 'surgery below T10' by VANDENBROUCKE *et al.* (22).

Hyperbaric ropivacaine provided as adequate sensory anesthesia as bupivacaine for this type of surgery. Motor block was more prominent in the bupivacaine group, and both sensor and motor block duration were longer in the bupivacaine group. No signs of TRI were noted after 3 days nor after 3 months. The authors concluded that hyperbaric ropivacaine may be a more suitable alternative for hyperbaric lidocaine especially when no prominent motor block is required.

#### INTRATHECAL ROPIVACAINE FOR LABOUR PAIN MANAGEMENT

With its lower propensity for motor block, ropivacaine has become a preferred option for labour pain management, as current practice in

obstetrics aims to provide effective pain relief while minimising motor blockade, therefore allowing ambulation during labour ('walking epidurals'). The introduction of the combined spinal-epidural technique fits in this 'philosophy'. It is an anesthesia technique by which analgesia is established with an initial spinal injection and adequate anesthesia is maintained with subsequent epidural injections. Motor block however often occurs after the initial injection.

Several authors have studied the use of ropivacaine, as part of a CSE technique, for labour pain management.

LEVIN *et al.* (23) compared ropivacaine (2 mg or 4 mg) and bupivacaine (2.5 mg), as part of a CSE technique. In all groups, the local anesthetic was combined with sufentanil (10 µg) for labor analgesia. Duration of anesthesia, pain scores, degree of motor block, foetal heart rate and other adverse events were assessed.

All patients were very satisfied with their analgesia and there were no reports of post dural puncture headache. Side effects, the most common being pruritis, were similar between the groups. Bromage scores of 0 were noted throughout the study in all groups. The authors concluded that 2 mg or 4 mg of spinal ropivacaine (combined with sufentanil) provided effective labour analgesia with rapid onset comparable to 2.5 mg bupivacaine (combined with sufentanil) without detectable motor block.

Low dose intrathecal ropivacaine (3 mg) with or without sufentanil (10 µg) was studied for labour pain analgesia by SONI *et al.* (24), as part of a CSE-anesthesia technique.

The duration of analgesia was significantly longer in the ropivacaine+sufentanil group, all parturients had satisfactory analgesia within five minutes after block placement (but satisfaction pain scores were higher in the ropivacaine + sufentanil group) and no patients showed evidence of motor block (which should facilitate ambulation during labour). There was no difference between the two groups in duration of labour.

As a conclusion, the authors said that low dose intrathecal ropivacaine provided effective analgesia during labour, but when a combination with sufentanil was made, both quality and duration anesthesia increased.

Similar results were published by HUGHES *et al.* (25). This group studied the intrathecal use of ropivacaine (2.5 mg) versus bupivacaine (2.5 mg), both with fentanyl 0.025 mg, and as part of a CSE-anesthesia technique.

The onset, duration and quality of analgesia were similar between both groups. The incidence of detectable motor block (using a modified Bromage Score) was significantly less in the ropivacaine+fentanyl group. Adverse events, the most frequent being pruritis, were similar in both groups. No foetal heart rate abnormalities or maternal hypotension were detected.

So the authors concluded that intrathecal ropivacaine in combination with fentanyl provided rapid and effective analgesia for labour pain management and that, in addition, there was significantly less motor block when compared to bupivacaine with fentanyl.

More recently, LIM *et al.* (26) compared ropivacaine 2.5 mg with bupivacaine 2.5 mg or levobupivacaine 2.5 mg as part of a CSE-technique in a controlled, double-blind, randomized study. Because of lack of conclusive evidence of compared small dose of intrathecal ropivacaine versus bupivacaine and levobupivacaine, the null hypothesis was assumed (no difference in potency), and 'equivalent' doses of each of the local anesthetics was used.

VAS pain scores were recorded before and after the block was placed. The degree of motor block and the highest sensory block were also noted. The primary outcome was duration of analgesia, which was the highest in the bupivacaine group but at the expense of a more frequent incidence of motor blockade.

Differences in patient satisfaction could not be detected in this study.

#### SPINAL LOCAL ANESTHETICS AND BARICITY

The baricity of a local anesthetic is the density of the solution relative to the density of the cerebrospinal fluid. A hypobaric/hyperbaric local anesthetic is defined as a solution with a density more than 3 standard deviations (SD) below/above mean human cerebrospinal fluid (CSF) density (27).

According to GREENE *et al.* (28), the extent of spinal anesthesia may be influenced by more than 20 demonstrated or hypothetical factors. Hyperbaric solutions spread under the influence of gravity, and patient position is accepted as the main determinant of subarachnoid spread. The extent of plain spinal anesthetic solutions is considered to be unpredictable and is not or less position dependent. Attempts to explain the unpredictability of extent of spinal block by plain local anesthetic solutions have resulted in many clinical reports.

Normal values of the human CSF densities have been studied, and important interindividual variations, especially between females and males (29), have been shown. Human CSF density not only varies with sex, but also with temperature, age, pregnancy and illness (27).

SCHIFFER *et al.* (30) studied the influence of CSF density on the extent of plain bupivacaine spinal anesthesia, and has shown that with a higher CSF density, a higher spinal block level could be expected.

Addition of dextrose to a local anesthetic increases the density of the solution and provides a more predictable and consistently higher sensory block (31).

Hyperbaric ropivacaine has been studied for several surgical indications (32), for C-section (13, 14) and in healthy volunteers (33).

In the study by McDONALD *et al.* (33) (18 healthy volunteers), three groups of volunteers received two times a spinal anesthesia, first with bupivacaine and 24h to 6 weeks later, with ropivacaine. The doses of the local anesthetics were 4, 8 or 12 mg, and the hyperbaric solutions were created by mixing 5 mg/ml of anesthetic with an equal volume of 10% dextrose, so that the final concentration was 2.5 mg/ml in 5% dextrose. Both local anesthetics provided dose dependent prolongation of sensory and motor block and the potency of ropivacaine was found to be approximately half of that of bupivacaine. The use of low dose of ropivacaine, as well as the use of healthy volunteers were noted as limitations of the study, so the authors recommended further investigations prior to the use of intrathecal ropivacaine.

WHITESIDE *et al.* (32) used hyperbaric ropivacaine (3 ml of ropivacaine 5 mg/ml in glucose 10 mg/ml or 50 mg/ml) for a variety of surgical procedures. The onset of analgesia was slightly more rapid and the block height was higher with the 50 mg/ml glucose concentration. The degree and duration of sensor and motor block were the same in both groups. The authors concluded that this study confirmed the benefit of adding glucose to solutions for intrathecal injection, and that the addition of glucose to clinically relevant concentrations of ropivacaine could provide reliable intrathecal anesthesia of intermediate duration.

The studies by CHUNG *et al.* (14) and KHAW *et al.* (13) were mentioned in the section '*Intrathecal ropivacaine for cesarean section*'.

MCLEOD *et al.* (27) recently compared the density of spinal anesthetic solutions of bupivacaine (2.5, 5 and 7.5 mg/ml), levobupivacaine (2.5,

5 and 7.5 mg/ml) and ropivacaine (2, 5, 7.5 and 10 mg/ml) with and without dextrose. He concluded that the density of local anesthetics decrease with increasing temperature and increases in a linear fashion with the addition of dextrose. Levobupivacaine 5 mg/ml has a significantly higher density compared to bupivacaine or ropivacaine 5 mg/ml at 23°C and at 37°C both with and without dextrose. This may be attributed to a higher sodium ion content and higher osmolality of levobupivacaine compared to bupivacaine or ropivacaine. There is a 13% additional contribution to osmolality by levobupivacaine compared with bupivacaine, because vials of levobupivacaine contain 7.5 mg/ml free base (26.0 mmol/l) whereas corresponding vials of bupivacaine contain 6.66 mg/ml free base (23.1 mmol/l) and ropivacaine 6.63 mg/ml free base (24.1 mmol/l).

Opioids are often added to spinal local anesthetics to improve anesthesia and prolong postoperative analgesia. Fentanyl e.g. is hypobaric and when added to a local anesthetic, the subsequent mixture will become more hypobaric (27).

#### INTRATHECAL ROPIVACAINE AND SAFETY

##### NEUROTOXICITY

Neurotoxicological studies should be performed before new drugs are introduced for spinal application in clinical practice. Such studies should include histopathological evaluation of the spinal cord after protracted spinal administration, as well as study of the effect of the drug on the spinal cord blood flow (SCBF).

IIDA *et al.* (34) reported a concentration-dependant vasoconstriction of spinal pial vessels in canine, while KRISTENSEN *et al.* (35) described a minor and transient decrease in SBCF after administration of 5 mg/ml of ropivacaine in rats, but this decrease was not significantly different from that in the saline group.

The intrathecal use of ropivacaine did not induce neurotoxic effects after intrathecal administration in dogs (36) and rabbits (37).

These results suggest that ropivacaine may be used for spinal anesthesia without important effects on SCBF.

Despite a long history of clinical use in spinal anesthesia, recent interest in neurotoxicity of local anesthetics has arisen due to concerns over reports of *cauda equina syndrome*, especially with the use of hyperbaric lidocaine 5% following spinal

anesthesia and *transient neurological symptoms (TNS)* or *arachnoiditis*.

*Cauda equina syndrome* may be due to an accumulation of hyperbaric spinal anesthetic in the area of the cauda equina nerves, resulting in local nerve damage (38, 39). The symptoms typically occur immediately after the intrathecal anesthesia has worn off and include numbness of the buttocks, leg weakness with reduced motor function and bladder and bowel incontinence.

Ropivacaine has not been associated with the development of cauda equina syndrome.

Several terms are used to describe *Transient Neurological Symptoms (TNS)* including Transient Radicular Irritation (TRI), Transient Lumbar Pain (TLP) and Transient Neurological Toxicity (TNT). The phenomenon of a dull, aching pain radiating into the lower back, buttocks and lower extremities following recovery from intrathecal anesthesia has been well documented (40, 41).

These symptoms were often associated with interventions in lithotomy position, which could result in stress in the musculature resulting in pain (42).

GANAPATHY *et al.* (43) were the first to report a case of TNS following low-dose (10 mg) intrathecal hyperbaric ropivacaine 1% (with addition of 0.5 ml dextrose 10 %) following knee arthroscopy, which lasted for 3 weeks. No paresthesia was mentioned during puncture in right lateral decubitus (2 attempts). Soon after turning supine, the patient reported severe low backache in the sacral area and discomfort was present throughout the surgery. The sensory block reached a level of T4 bilaterally and surgery was performed without any additional analgesics nor sedation. The patient reported no pain or nausea in the PACU, and the patient had no motor block in both legs on arrival. The morning after surgery, the patient reported moderate to severe headache and nausea. She also had neck pain and severe back ache, which worsened during coughing. The pain persisted postoperatively for several days, radiating to her buttocks, back of the thighs and calves. The patient recovered gradually over a prolonged period and 20 days after the intervention, she had only a mild ache in the sacrum, which improved further over the following 6 weeks.

*Arachnoiditis* is an inflammatory process, which may occur as a result of a number of factors, such as trauma, surgery, infection or the intrathecal administration of a number of compounds including anesthetics. This can result in the adhesion of the nerve roots in the spinal cord and cauda equina.

Symptom onset may be immediate or may take several months after an event before they manifest. This condition can result in a progressive loss of motor and sensor function leading to paraplegia, quadriplegia and death (44).

Ropivacaine has not been associated with the development of arachnoiditis.

#### POST DURAL PUNCTURE HEADACHE (PDPH)

PDPH is thought to be the result of leakage of CSF due to dural puncture with resultant loss of CSF pressure. It causes significant morbidity, can mostly be treated with mild analgesics and resolves spontaneously over a few days, although there are reports of longer lasting cases. Obligatory, differential diagnosis with subdural hematoma should be done.

Limited data are available on this topic, most studies indicate that PDPH is not drug related and that the puncture technique as well as the needle gauge are more important (45).

Ropivacaine seems to be well tolerated, with no greater incidence of PDPH than that reported for other local anesthetics used for intrathecal anesthesia (15, 16, 23, 24).

#### INTRATHECAL ROPIVACAINE FOR CANCER PAIN MANAGEMENT

Only limited, contradictory data are available on the intrathecal use of ropivacaine for cancer pain management.

A patient with a neuropathic pain syndrome following surgery for gynaecological cancer, and successfully treated with an intrathecal catheter with a continuous infusion of bupivacaine and switched after 3 days to ropivacaine, was described by MERCADANTE *et al.* (46). No differences were noted between bupivacaine and ropivacaine in pain intensity, sensory disturbance, motor weakness or the number of boluses required. The authors said that long-term studies in a larger sample of cancer patients were necessary to confirm this preliminary observation, but that in this case, ropivacaine was well tolerated and effective.

In a case report from KSHATRI *et al.* (47) a patient with intractable pain due to a metastatic carcinoma of the cervix, with subsequent intestinal obstruction necessitating intervention, was presented. The patient received a spinal bupivacaine and morphine infusion with an external pump.

Bupivacaine was switched to ropivacaine in order to improve (preserve) the motor function at home. The patient was discharged with a PCA device administering a background infusion of 1 ml/h ropivacaine 0.2% (2 mg/ml) with 0.002% morphine and 0.0002% epinephrine. Self-administration was possible by means of 0.5 ml boluses every 30 minutes. Ambulation was maintained with walking support, until the disease progressed almost 6 weeks later.

The first double-blind, randomised study on this topic was presented by DAHM *et al.* (48). They compared the intrathecal use of ropivacaine with bupivacaine in the treatment of refractory cancer or noncancer pain. 12 patients (9 with cancer pain) received a 7 day-infusion of one the local anesthetics before being switched to the other agent. The daily dose of ropivacaine was higher than bupivacaine for a similar degree of pain relief and also the cost was significantly higher with ropivacaine. The authors concluded that this study in a small group of patients could not support the use of intrathecal ropivacaine (5 mg/ml) for the relief of refractory malignant or non-malignant pathologic pain conditions.

#### CONCLUSION

Ropivacaine has recently been approved for the intrathecal route of administration in the EU. Since its launch in 1996, a broader clinical experience has become available on its use for spinal anesthesia. Studies with intrathecal ropivacaine have demonstrated good tolerability and efficacy, without any neurotoxic effects. Often different solutions in several concentrations and this for a wide variety of indications are presented, which can be confounding. It is also important to look at the chosen endpoints and assessment parameters before comparing different studies on this matter.

In the 'quest' for an ideal local anesthetic for spinal anesthesia, the lower lipid solubility of ropivacaine with an associated greater sensor motor separation, could offer some advantages in day-case anesthesia, were early ambulation and voiding could be translated into earlier discharge.

The use of additives, usually opioids or clonidine, to low doses of intrathecal ropivacaine has been studied for several indications, and seems to emphasize the possibility to provide adequate intrathecal anesthesia with low doses of ropivacaine, without compromising the benefits of early mobilization and voiding.

There is also published data on the use of hyperbaric ropivacaine for spinal anesthesia, but this solution is not commercially available for the moment.

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