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REVIEW

Prilocaine hydrochloride 2% hyperbaric solution for intrathecal injection: a clinical review

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Abstract: Prilocaine is a local anesthetic characterized by intermediate potency and duration and fast onset of action. As hyperbaric formulation of 5% solution, it was introduced and has been successfully used for spinal anesthesia since 1960. A new formulation of 2% plain and hyperbaric solution is currently available in Europe. Because of its lower incidence of transient neurological symptoms, prilocaine is suggested as substitute to lidocaine and mepivacaine in spinal anesthesia for ambulatory surgery, as well as a suitable alternative to low doses of long-acting local anesthetics. The National Library of Medicine database, the Excerpta Medica database, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials database, were searched for the period 1970 to September 2016, with the aim to identify studies evaluating the intrathecal use of 2% prilocaine. A total of 13 randomized clinical trials (RCTs), 1 observational study, 2 dose finding, and 4 systematic reviews has been used for this review. The studies evaluated showed that 2% hyperbaric prilocaine due to a favorable anesthetic and safety profile is an alternative drug to lidocaine and mepivacaine for spinal anesthesia of intermediate or short duration. In comparison with plain solutions, hyperbaricity remarkably accelerates the onset and offset times of intrathecal 2% prilocaine. Literature suggests a dose ranging between 40 and 60 mg of prilocaine for lower extremities and lower abdominal procedures lasting up to 90 min, whereas a dose ranging from 10 to 30 mg is appropriate for perineal surgery. Readiness for discharge occurs in ~4 h from spinal administration.

Keywords: short acting local anesthetic, transient neurologic symptoms, postoperative urinary retention, spinal anesthesia, day surgery

Introduction

In the last decade, as the trend toward ambulatory surgery continues, interest in available drugs for outpatient spinal anesthesia has increased accordingly. An ideal outpatient spinal anesthetic would provide rapid sensory and motor block, predictable regression and a low incidence of side effects.[1] For many years this profile has been fulfilled by lidocaine but, in 1993, "transient neurologic symptoms" (TNS) were described as adverse events in patients after a single spinal injection of lidocaine.[2,3] TNS are known to occur even with other local anesthetics, such as mepivacaine (AstraZeneca, Cambridge, UK) and procaine (Hospira, Inc., Lake Forest, IL, USA).[4–6] Nevertheless, the highest risk of TNS is related to spinal lidocaine, and therefore its use for spinal anesthesia has been questioned.

Small doses of long-acting local anesthetics such as bupivacaine (AstraZeneca), levobupivacaine (AbbVie Inc., North Chicago, IL, USA), and ropivacaine (AstraZeneca) have been used for spinal anesthesia in ambulatory surgery. With the use of large doses

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of long-acting local anesthetics, delay of discharge emerged as a growing problem, although small doses demonstrated a wide variability in block duration and failure rate.[7–8]

Due to its intermediate duration of action and the lower incidence of TNS, prilocaine (Sintetica SA, Mendrisio, Switzerland) has been proposed as a valuable alternative to lidocaine as well as to small doses of long-acting local anesthetics for short procedures performed under spinal anesthesia.

The purpose of this review is to summarize the available data on the use of prilocaine for spinal anesthesia, focusing on 2% hyperbaric solutions, to highlight the safety and the effectiveness of its use for ambulatory and short time surgeries.

Methods

The National Library of Medicine database (MEDLINE), the Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews (CINAHL), and the Cochrane Central Register of Controlled Trials database (CENTRAL) were searched for the time period 1970 to September 2016, with the aim to identify studies evaluating the intrathecal use of prilocaine, rather than studies that compared its intrathecal administration to another anesthetic, in terms of safety, efficacy, and readiness for discharge after ambulatory surgery. Search strategies included the terms "prilocaine" with "spinal anesthesia" and "ambulatory surgery." References of all retrieved articles were manually searched to identify any other study not found in the electronic search.

The quality of the randomized controlled trials (RCTs) included in this review has been reported using the Jadad Scale.[9] Studies were excluded if they were conference proceedings not followed up by full publication. Only English-language articles and articles with sufficiently detailed abstract translated into English were included in the review. Randomized trials with a Jadad Scale lower than 3 were excluded.

Results

A total of 13 RCTs, 1 observational study, 2 dose finding, and 4 systematic reviews has been finally used for this review. The main clinical characteristics of the RCTs using 2% prilocaine and their Jadad Scale are detailed in Table 1.

Prilocaine

Prilocaine is an amide-type local anesthetic characterized by intermediate potency and duration and fast onset of action. Unlike lidocaine, which is a tertiary amine, prilocaine is a secondary amine, which has relevant advantages in terms of toxicity. Prilocaine has the highest clearance of all amino-amide local anesthetics, more than twice the clearance of lidocaine.

Together with its larger distribution volume, this feature is responsible for the considerably lower prilocaine plasma concentration compared to lidocaine and mepivacaine after regional anesthesia.[10] As a consequence, prilocaine reaches toxic blood concentrations very rarely, and the recommended maximum dose is about twice the maximum dose of lidocaine.

The amide-linked local anesthetics are degraded by the hepatic endoplasmic reticulum. In the liver, prilocaine is primarily metabolized by amide hydrolysis to σ-toluidine and *N*-propylalanine. σ-Toluidine is subsequently hydroxylated to 2-amino-3-hydroxytoluene and 2-amino-5-hydroxytoluene, metabolites responsible for the occurrence of methemoglobinemia.[11] A high dose of prilocaine (>600 mg) is needed to cause a clinically apparent methemoglobinemia in the healthy adult.[12] The low doses of hyperbaric prilocaine used in spinal anesthesia do not produce a sufficient amount of σ-toluidine thereby avoiding additional risk for the patient.

Prilocaine hydrochloride was synthesized in 1953 and submitted to extensive pharmacological and toxicological investigations since the 1960s.

One of the first publications reporting about the intrathecal use of prilocaine appeared in 1965.[13] The drug (75 mg, 5% concentration) was administered to 106 patients to achieve spinal anesthesia for transurethral prostate resection. The quality of the block was adequate, safe, and satisfactory.

Prilocaine was never approved for intrathecal administration in the USA, whereas it was used as a standard drug for spinal anesthesia in UK until 1978 and in France until 1998. Despite its favorable anesthetic profile, these products, Citanest 5% Heavy (AstraZeneca) and Citanest Rachianesthésie (Laboratoires Dentoria, Gentilly, France), were withdrawn from the market for commercial reasons and because of stability problems related to the production procedures.[14,15]

Since 2005, in Germany by AstraZeneca and in Switzerland by Sintetica SA, 2% prilocaine hydrochloride has been developed as plain and hyperbaric solution, respectively.

2% Hyperbaric prilocaine

The solution of 2% hyperbaric prilocaine developed in Switzerland by Sintetica, contains 6% glucose and has a density ranging from 1.024 to 1.027 g/g at 20°C, corresponding to a mean density value of 1.021 at 37°C, higher than the cerebrospinal fluid density at 37°C.

It is well known that baricity of the injected drugs mainly affects their spinal spread.[16,17] These solutions lead to a faster spread to a higher median dermatomal level with less variation in maximum sensory and motor block in comparison with isobaric solutions.[18,19] A more predictable and reliable block follows after hyperbaric than plain solutions.[20]

The distribution of hyperbaric spinal anesthesia also influences the duration of the block. With the same dose of hyperbaric bupivacaine, the spinal block lasted longer in patients with a restricted block.[21] For this property, several local anesthetics have been formulated as hyperbaric solutions for intrathecal administration.[17]

To investigate the advantages of the hyperbaric formulation versus plain prilocaine, in 2010 Camponovo et al published a randomized, noninferiority study.[22] The authors compared the efficacy in inducing sensory block to T10 of two different intrathecal doses of 2% hyperbaric prilocaine (60 and 40 mg) and one dose of 2% plain prilocaine (60 mg) in outpatients undergoing elective short-duration surgery (<60 min). Both 60 and 40 mg of 2% hyperbaric prilocaine induced a T10 level of sensory block with significantly shorter onset times than 60 mg of 2% plain prilocaine. On recovery from spinal anesthesia, the effects of the hyperbaric solutions ceased more rapidly than the plain solution. In particular, 40 mg of 2% hyperbaric prilocaine allowed a complete recovery from the motor block (i.e., time to unassisted ambulation) in 90 min in comparison with 121 and 160 min for Group Hyperbaric 60 and Plain 60. In conclusion, 2% hyperbaric prilocaine remarkably improves the well-known features of the plain solution and shows good suitability for short-duration surgery. Motor and sensory blocks are established faster; the anesthetic is fixed earlier, and patients recover faster after hyperbaric than after spinal plain prilocaine.

Hyperbaric prilocaine 2% was first compared by Ratsch et al with 0.5% hyperbaric bupivacaine.[23] Eighty-eight patients scheduled for lower limb surgery lasting a maximum of 45 min under spinal anesthesia were randomly allocated to receive either 15 mg of 0.5% hyperbaric bupivacaine or 60 mg 2% hyperbaric prilocaine. Both groups were comparable in reaching the required analgesic level of T12, as well as in block intensity and onset times of maximum sensory block. A T12 analgesic level was maintained for 60 min with prilocaine versus 120 min with bupivacaine, whereas regression of the motor block took 135 versus 210 min and time for spontaneous micturition was 306 versus 405 min for prilocaine and bupivacaine, respectively. The two study drugs achieved the equivalent quality of sensory/motor blocks, allowing adequate surgical anesthesia for at least 1 h, as well as the comparable occurrence of undesired side effects. Nevertheless, 2% hyperbaric prilocaine was superior to 0.5% hyperbaric bupivacaine regarding faster offset, faster time to first spontaneous voiding, faster recovery-room and home discharges.

The use of hyperbaric solutions can further allow restricting the block mostly to the operative side.[24] Unilateral spinal anesthesia allows minimizing the extent of sympathetic blockade, resulting in minimal impairment of cardiovascular homeostasis and thus reducing the incidence of clinically relevant hypotension to 5%–7%.[25] A more profound motor block to the operative side was also enhanced, increasing patient satisfaction and resulting in a significant acceleration of patient discharge, making unilateral spinal anesthesia an interesting option for outpatient surgery.

For this purpose, Manassero et al compared the anesthetic profile of unilateral and conventional bilateral spinal anesthesia with the same dose (50 mg) of hyperbaric 2% prilocaine in inguinal herniorrhaphy.[26] In the unilateral group, spinal anesthesia was performed on lateral decubitus which was maintained for 10 min. With this short time, only 12.5% of the patients achieved a restrict unilateral spinal block (sensory block below S1 in the nonoperated limb) 20 min after spinal anesthesia. Nevertheless, time to voiding was faster in the unilateral (220±47 min) than in a conventional group (249±51 min), demonstrating that attempting unilateral spinal block may improve the time to first voiding and so the time to home discharge. No episodes of urinary retention occurred in either group. The study confirmed prilocaine as an effective spinal anesthetic for day-case surgery showed a dose of 50 mg hyperbaric adequate for inguinal repair lasting up 60 min.

Perianal surgery

A dose finding study was performed by Gebhardt who tested three dosages of 2% hyperbaric prilocaine in perianal outpatient surgery. The authors injected 10, 20, or 30 mg in sitting position; then patients were brought into lithotomy position after 10 min. The results suggested 10 mg as the recommended dose in procedures lasting no longer than 40 min, because of sufficient analgesia, preserved motor function of the lower extremities, shorter voiding (173±31 min) and discharge time (199±39 min). None of the patients suffered from urinary retention.[27]

Accordingly, 10 mg of 2% hyperbaric prilocaine was then compared by Gebhardt with 20 mg of 4% hyperbaric mepivacaine in perianal outpatient surgery. The recovery profile from spinal anesthesia with prilocaine 10 mg was confirmed: prilocaine led to shorter time to first spontaneous micturition

Table 1 Main results of randomized controlled trials published about prilocaine 2%

Author	Jadad Scale	Drugs	Additives	Pts	Setting	Sensory block onset (min)	Motor block onset (min)
Ambrosoli et al[31]	3	40 mg 2% H prilocaine	None	50	Arthroscopic knee surgery	6.0 (5.0–10.0) (in the femoral nerve distribution)	6.5 (4.0–10.0) (in the femoral nerve distribution)
		US-guided femoral-sciatic nerve block with 2% mepivacaine 25 mL	None	50		NR	NR
Aguirre et al[32]	5	60 mg 2% H prilocaine	None	70	Arthroscopic knee surgery	4.2±1 (T10 dermatome)	NR
		12 mg 0.4% P ropivacaine	None	70		5.2±1 (T10 dermatome)	NR
Manassero et al[26]	3	50 mg 2% H prilocaine lateral position	None	40	Inguinal herniorrhaphy	NR	At 10 min 96%* pts Bromage=3 in the operated limb
		50 mg 2% H prilocaine sitting position	None	40		NR	At 10 min 58% pts Bromage=3 in the operated limb
Kaban et al[29]	3	30 mg 2% H prilocaine	20 µg fentanyl	25	Perianal surgery	4.6±1.3* (L1 dermatome)	NR
		7.5 mg 0.5% H bupivacaine	20 µg fentanyl	25		5.9±1.9 (L1 dermatome)	NR
Gebhardt et al[28]	4	10 mg 2% H prilocaine	None	80	Perianal surgery	NR	NR
		20 mg 4% H mepivacaine	None	80		NR	NR
Akcaboy et al[37]	5	50 mg 2% H prilocaine	25 µg fentanyl	30	Transurethral resection of prostate surgery in geriatric patients	7.1±1.9 higher dermatome	Bromage 2 (1–3)* (at the time of reaching highest sensory block)
		4 mg 0.5% H bupivacaine	25 µg fentanyl	30		7.6±1.3 higher dermatome	Bromage 1 (0–3) (at the time of reaching highest sensory block)
Black et al[36]	5	20 mg 2% P prilocaine	20 µg fentanyl	25	Arthroscopic knee surgery	11.3 (2.5–55)* higher dermatome	NR
		7.5 mg 0.5% P bupivacaine	20 µg fentanyl	25		20.0 (7.5–60) higher dermatome	NR
Camponovo et al[22]	4	40 mg 2% H prilocaine	None	30	Surgical procedures lasting <60 min	9±5[a] (T10 dermatome)	8±5[a] (Bromage≥2)
		60 mg 2% H prilocaine	None	30		7±4[a](T10 dermatome)	8±3[a] (Bromage≥2)
		60 mg 2% P prilocaine	None	30		14±7 (T10 dermatome)	12±5 (Bromage≥2)
Hendriks et al[35]	5	50 mg 2% P prilocaine	None	36	Arthroscopic knee surgery	2 (2–10) (L1 dermatome)	5 (2–15) (Bromage=2)
		50 mg 2% P Articaine	None	36		2 (2–15) (L1 dermatome)	5 (2–15) (Bromage=2)
Rätsch et al[23]	5	60 mg 2% H prilocaine	None	44	Lower extremity procedures lasting up to 45 min	5±3 (T12 dermatome)	10±10 (Bromage=3)
		15 mg 0.5% H bupivacaine	None	44		4±8 (T12 dermatome)	10±10 (Bromage=3)

Sensory block resolution (min)	Motor block resolution (min)	Time to micturition (min)	POUR	Fluid management	TNS	Main results
NR	285 (240–330)* (unassisted ambulation)	225 (220–300)	0	500 mL crystalloids before SA; no intra-operative fluids unless hypotension	0	Discharge home was faster after intrathecal anesthesia with 40 mg hyperbaric prilocaine than after femoral-sciatic nerve blockade following day-case knee arthroscopy
NR	328 (280–362) (unassisted ambulation)	220 (135–290)	0		/	
120 (120–180) (T12 regression)	180 (169–240)* (Bromage=1)	250 (231–300)	0	4 mL/kg/h of crystalloids throughout the procedure	0	The recovery of motor block was faster after 2% prilocaine compared with 0.4% plain ropivacaine. Discharge time was similar between the two groups
120 (70–180) (T12 regression)	240 (180–300) (Bromage=1)	270 (235–320)	0		0	
156±30 (S2 regression) in the operated limb	115±26 (Bromage=0) in the operated limb	220±47*	0	7 mL/kg crystalloids before SA; 4 mL/kg/h until spontaneous micturition	0	In day-case inguinal herniorrhaphy, attempting unilateral spinal anesthesia with 50 mg hyperbaric 2% prilocaine produced faster time to voiding
158±26 (S2 regression) in the operated limb	108±24 (Bromage=0) in the operated limb	249±51	0		0	
133±41* (S3 regression)	136±53* (unassisted ambulation)	152±104	1	7 mL/kg crystalloids before SA; no intra-operative fluids unless hypotension	0	Prilocaine 30 mg+20 µg fentanyl provides faster sensory block resolution and home readiness compared to 7.5 mg bupivacaine+20 µg fentanyl
200±64 (S3 regression)	172±82 (unassisted ambulation)	172±130	1		0	
NR	168 (98–252)	178 (110–254)	0	A maximum of 500 ml crystalloids	0	Both, hyperbaric mepivacaine and prilocaine can be used at dosage of 0.5 mL each for spinal anesthesia in perianal outpatient surgery. TNS was lower with prilocaine.
NR	175 (100–300)	195 (130–305)	0		6	
NR	158±12 (Bromage=0)	Transurethral catheter		8 mL/kg/h of crystalloids throughout the procedure	NR	Intrathecal 4 mg bupivacaine+25 µg fentanyl provided adequate spinal anesthesia with shorter block duration than intrathecal 50 mg prilocaine+25 µg fentanyl for day case transurethral resection of prostate surgery in geriatric patients
NR	110±14* (Bromage=0)	Transurethral catheter			NR	
97 (90–115)* (L4 regression)	75%[a] pts Bromage=0 at 1 h	205 (185–220)*	0	NR	0	Prilocaine showed a faster attainment and resolution of block, together with greater hemodynamic stability
280 (207-not computable) (L4 regression)	None pts Bromage=0 at 1 h	275 (250–300)	0		0	
110±35* (complete regression)	92±36* (Bromage=0)	195[a] (60)	0	7 mL/kg crystalloids before SA	0	2% hyperbaric prilocaine showed faster times to motor block onset and shorter duration of surgical block
132±34* (complete regression)	118±37* (Bromage=0)	218[a] (56)	0		0	
163±42 (complete regression)	157 (41) (Bromage=0)	277 (85)	0		0	
56 (20–153) (for 2-dermatome regression)	184±46 (Bromage=0)	227±45	3	A maximum of 500 mL crystalloids	0	Articaina showed a faster full motor function recovery and a shorter time for spontaneous micturition
61 (24–104) (for 2-dermatome regression)	140±33* (Bromage=0)	184±39[a]	1		1	
240±90* (S1 regression)	135±90* (Bromage=0)	306±56[a]	0	1,000 mL crystalloids before SA	0	Hyperbaric 2% prilocaine is superior to hyperbaric 0.5 bupivacaine due to a shorter effect profile with equivalent quality of block
360±60 (S1 regression)	210±90 (Bromage=0)	405±125	2		0	

(*Continued*)

Table 1 (*Continued*)

Author	Jadad Scale	Drugs	Additives	Pts	Setting	Sensory block onset (min)	Motor block onset (min)
De Weert et al[50]	3	80 mg 2% P prilocaine	None	35	Surgical procedures lasting <60 min	NR	NR
		80 mg 2% P lidocaine	None	35		NR	NR
Østgaard et al[51]	5	80 mg 2% P prilocaine	None	50	Urologic surgical procedures lasting <60 min	13.4±4 (higher dermatome)	NR
		80 mg 2% P lidocaine	None	50		14.5±6 (higher dermatome)	NR
Hampl et al[47]	4	50 mg 2% H (7.5% glucose) prilocaine	None	30	Gynecologic short surgical procedures	NR	4 (1–4)
		50 mg 2% H (7.5% glucose) lidocaine	None	30		NR	4 (2–4)
		12.5 mg 0.5% H (7.5% glucose) bupivacaine	None	30		NR	4 (1–4)

Note: [a]Significant difference. *Statistically significant.
Abbreviations: H, hyperbaric; NR, not reported; P, plain; POUR postoperative urinary retention; Pts, patients; SA, spinal anesthesia; TNS, transient neurologic symptoms.

(178 min with prilocaine vs 195 min with mepivacaine) as well as faster discharge time (192 vs 220 min). In the prilocaine group, the time to first analgesic administration was 173 min.[28]

In day-case perianal surgery, Kaban compared 30 mg 2% hyperbaric prilocaine with fentanyl 20 μg versus 7.5 mg of 0.5% hyperbaric bupivacaine with fentanyl 20 μg.[29] Time to unassisted ambulation, time to sensory block resolution, and time to home discharge were significantly shorter in the prilocaine group than in the bupivacaine group. One patient in each group had urinary retention. Compared to the study by Gebhardt, prilocaine 30 mg showed a shorter time to urinary voiding (152±104 vs 211±33) and to discharge (155±100 vs 229±32). As the author noticed, in the study by Gebhardt, the patients waited in the sitting position for 10 min after the spinal injection, whereas in the study by Kaban the patients remained in sitting position for only 2 min after the injection. As a consequence, in the first case, the anesthetic spread a median of 5 dermatomes from S5 upwards (max to L4 dermatome), whereas the anesthetic spread up to T9 dermatome in the second case. As the duration of spinal nerve blockade is inversely related to the intrathecal spread of the same anesthetic dosage,[21] in the study by Kaban spinal recovery resulted faster.

The author also highlighted that in the prilocaine group, despite the shorter sensory block recovery (133±41 min to S3 dermatome resolution), the time to first analgesic intake was almost delayed (192 min), promoting fentanyl 20 μg as a suitable adjuvant with the aim to increase the quality of the sensory block without prolonging motor block and time to micturition.

Arthroscopy knee surgery

In arthroscopy knee surgery, Guntz et al performed a dose finding study using 2% hyperbaric prilocaine.[30] With the up-and-down sequential allocation technique, Guntz estimated the effective dose 90 of 2% hyperbaric prilocaine to be 38.5 mg for patients undergoing knee arthroscopy under spinal anesthesia. The author suggested 40 mg as the dose required to provide an adequate sensory (T12) and motor block (Bromage=3) in 92% of the patients, 15 min after spinal injection. Moreover, in the same study 40 mg of 2% hyperbaricc prilocaine showed hemodynamic stability, motor block regression in less than 90 min (87 min), and spontaneous voiding in all patients enrolled leading to a time of eligibility for home discharge of 205 min.

In day-case knee arthroscopy, 40 mg was the dose chosen by Ambrosoli et al to compare intrathecal blockade with 2% hyperbaric prilocaine versus ultrasound-guided femoral-sciatic nerve blockade with mepivacaine 2%.[31] Sensory and motor blockade recovered sooner after prilocaine spinal anesthesia. Time to home readiness was faster after intrathecal blockade than after peripheral nerve blockade, while time to micturition was not different between the two techniques (225 min after intrathecal anesthesia vs 220 min after periph-

Sensory block resolution (min)	Motor block resolution (min)	Time to micturition (min)	POUR	Fluid management	TNS	Main results
127±59 (for 2-dermatome regression)	166±45 (Bromage=0)	NR	NR	500 mL 0.45% saline/3.3% glucose solution before SA	0	Prilocaine results in a lower incidence of transient neurological symptoms than lidocaine intrathecally and therefore it is more suitable for short surgical procedures
105±39 (for 2-dermatome regression)	130±30 (Bromage=0)	NR	NR		7	
221±49 (S1 regression)	197±42 (Bromage=0)	NR	NR	500 mL crystalloids before SA	2	Isobaric prilocaine has a longer duration of action than an equal dose of lidocaine and may be an alternative drug for spinal anesthesia of intermediate or short duration. TNS occurred also after the isobaric prilocaine spinal anesthesia; there may be an indication of a lower frequency
181±48 (S1 regression)	153±46 (Bromage=0)	NR	NR		7	
128±38 (S1 regression)	165±37 (Bromage=0)	253±55	NR	NR	9	Prilocaine was associated with a significantly lower incidence of TNS compared with lidocaine. The duration of action was comparable to that of lidocaine. Prilocaine might be appropriate to use in place of lidocaine for spinal anesthesia
127±33 (S2 regression)	155±40 (Bromage=0)	238±57	NR		1	
172±42 (S2 regression)	200±48 (Bromage=0)	299±85	NR		0	

eral nerve blockade). The study confirmed prilocaine 40 mg to be adequate for knee arthroscopy in 96% of the patients.

In the same type of ambulatory surgery, Aguirre et al compared 60 mg of 2% hyperbaric prilocaine with 12 mg of 0.4% plain ropivacaine.[32] The offset of motor block was faster after intrathecal administration of prilocaine (180 vs 240 min). Nevertheless, 60 mg of prilocaine did not show any difference regarding first spontaneous voiding and discharge times between the two groups (330 min with prilocaine vs 335 min with ropivacaine). According to Manassero et al, this result was mainly influenced by the high selected dose of prilocaine (60 mg) for knee arthroscopy and, moreover, not equipotent to ropivacaine 12 mg.[33,34]

Hendriks compared 50 mg of 2% plain prilocaine to 50 mg of 2% plain articaine in day-case knee arthroscopy.[35] Recovery of motor function (140±33 vs 184±46 min) and time to spontaneous voiding (184±33 vs 227±45 min) were significantly shorter with articaine.

Using the plain prilocaine formulation, Black compared a remarkably low dose of 20 mg with fentanyl 20 μg versus 7.5 mg plain bupivacaine with fentanyl 20 μg in knee arthroscopies with median time elapsed from intrathecal drug administration to arrival in the recovery area of 35 (20–55) min. Time to micturition, motor, and sensory block regression was significantly shorter in prilocaine than in bupivacaine group.[36] A total of six patients (12%) complained of pruritus.

Urologic procedures

In geriatric patients undergoing day-case transurethral resection of the prostate (TURP) surgery, Akcaboy matched intrathecal administration of a conventional dose of 50 mg 2% hyperbaric prilocaine plus fentanyl 25 μg and a low dose of 4 mg 0.5% hyperbaric bupivacaine plus fentanyl 25 μg.[37] Dermatome T10 was the desired level of analgesia. Despite the very low dose of bupivacaine, none of the patients in either group manifested block failure or pain during the entire procedure which lasted a mean of 60 min. Spinal anesthesia with bupivacaine recovered sooner, while adverse events such hypotension and bradycardia were observed more frequently in the prilocaine group. A total of six patients (12%) complained of pruritus.

The author concluded 4 mg bupivacaine plus fentanyl 25 μg are comparable to 50 mg prilocaine plus fentanyl 25 μg in TURP. Nevertheless, the author commented that the comparison might be affected by not equipotent dose selection.

Prilocaine and postoperative urinary retention

It is well known that, after spinal anesthesia, spontaneous voiding is the last function to recover after motor block resolution. It may not be expected until regression of sensory blockade reaches S3 dermatome level. Moreover, the contents of the bladder can exceed the cystometric capacity before the reappearing of its normal function, leading to an acute

postoperative urinary retention (POUR).[38] Compared to an equipotent dose of long-acting spinal anesthetic, prilocaine showed a more rapid return of bladder function associated with lower incidence of POUR, as expected with shorter-acting drugs.[23,36]

In 25 day-case perianal surgeries, Kaban showed one case of POUR after intrathecal 30 mg of 2% hyperbaric prilocaine with fentanyl 20 μg.[29] Using 40 or 50 mg 2% hyperbaric prilocaine, mean time to first micturition ranged from 195 to 249 min with no cases of POUR in 160 patients.[22,26,31]

With 60 mg of hyperbaric 2% prilocaine, Aguirre, Camponovo and Ratsh showed no case of POUR in 144 lower limb ambulatory surgeries, reporting mean times to first micturition ranging between 218 and 306 min.[22,23,32] Nevertheless, after a properly designed observational study, using the same dosage of intrathecal 2% hyperbaric prilocaine, Kreutziger et al showed a high rate of urinary retention (23%) in 86 relatively low-risk patients (mean age 46 years without urogenital pathologies, lower limb minor orthopedic procedures). As per the study protocol, catheterization was planned when bladder volume exceeded 600 mL together with the inability to micturate.[39] To avoid a dangerous bladder over-distension, the author outlined the importance to use restrict criteria for catheterization based not on a clinical judgment but on ultrasound estimation of the bladder volume.[40] If spontaneous micturition should remain a criterion for discharge after day-case prilocaine, spinal anesthesia is still debated. Risk factors for postoperative urinary retention are well identified.[41] Short-acting spinal anesthetics for low-risk patients and low-risk procedures, are associated with minimal risk of urinary retention, and the patient could be discharged home without the need to void before discharge.[42] Patients at high risk of urinary retention should be managed with ultrasound bladder volume estimation, requiring voiding before discharge or catheterization if the bladder volume exceeded 600 mL.[2] Any case, providing adequate but not excessive intravenous fluid perioperatively may overall, minimize the risk for POUR (Table 1).[42]

Prilocaine and TNS

The symptoms of TNS can appear in few hours postoperatively or within the first 24 h, even after recovery from an uneventful spinal block. These symptoms consist of pain originating in the gluteal region and radiating to lower extremities.[43–46]

Prilocaine was extensively examined especially for the incidence of TNS after subarachnoid use. In a prospective, double-blinded study, Hampl et al compared prilocaine to lidocaine and bupivacaine for the relative risk of TNS.[47] Spinal anesthesia was induced with 2.5 mL 2% lidocaine in 7.5% glucose, 2% prilocaine in 7.5% glucose, or 0.5% bupivacaine in 7.5% glucose. Symptoms of TNS were observed for 9 patients (30%) receiving lidocaine, 1 patient receiving prilocaine (3%), and none receiving bupivacaine. The difference in the incidence of TNS between lidocaine and prilocaine was statistically significant.

Two hundred patients were randomly treated by Martìnez-Bourio et al with 5% hyperbaric prilocaine or 5% hyperbaric lidocaine. The dose for spinal anesthesia was calculated in relation to the type of procedure and patient height (mean dose: 68.6 mg for prilocaine and 67.7 mg for lidocaine). TNS occurred within 12–24 h in 1 patient (1%) in the prilocaine group and 4 patients (4.2%) in the lidocaine group and disappeared in both groups within 48–72 h. The difference was not significant, also due to the low incidence of the symptoms in this population.[48]

A survey on about 5,000 spinal anesthesia performed with 1 mg/kg 2% prilocaine did not report any case of TNS.[49]

Another study compared 80 mg of 2% prilocaine plain solutions versus 2% lidocaine plain solutions for spinal anesthesia.[50] Seven patients (20%) treated with lidocaine had TNS within 24 h after surgery and symptoms disappeared within 4 days. In contrast, no patient in the prilocaine group reported TNS and the difference was statistically significant.

With the same doses of plain prilocaine and lidocaine formulation (80 mg, 2% solution), Østgaard et al performed a study on 100 patients scheduled for elective short urologic procedures.[51] Nine patients fulfilled the criteria for TNS: 7 in the lidocaine group (14%) and 2 in the prilocaine group (4%). Symptoms resolved within 2–3 days, but the difference was not significant. Moreover, both studies showed prilocaine as a same duration of action than an equal dose of lidocaine resulting an alternative drug for spinal anesthesia of intermediate or short duration.

The risk of TNS after spinal anesthesia with local anesthetics was evaluated by a systematic review of randomized controlled trials.[52] A total of 29 studies (2813 patients) was evaluated in the analysis: the incidence of TNS was 16.9% after lidocaine, 19.1% after mepivacaine, 1.1% after bupivacaine, and 1.7% after prilocaine. The relative risk for TNS resulted to be 6.7- and 5.5-fold higher for lidocaine than bupivacaine and prilocaine, respectively. Furthermore, data showed that baricity and concentration of the local anesthetic have no significant influence on the occurrence of TNS.

A similar systematic analysis was performed to compare the frequency of TNS after spinal anesthesia with lidocaine versus other local anesthetics in adult surgical patients.[53,54] Fourteen

studies enrolling a total of 1,349 patients were examined: 117 patients developed TNS. It was evinced that all these drugs can cause TNS. However, the relative risk for developing TNS after spinal anesthesia with lidocaine was 4.35, as compared to other local anesthetics (bupivacaine, prilocaine, procaine, levobupivacaine, and ropivacaine). Finally, an updated analysis was conducted in 2009, confirming the lower risk of TNS related to spinal prilocaine compared to lidocaine.[55]

Conclusion

Due to its predictable intermediate duration of action and the low incidence of TNS (Evidence Ia[56]), spinal 2% hyperbaric prilocaine can be successfully used to provide anesthesia for a variety of day-case procedures, resulting an alternative drug to lidocaine and mepivacaine for spinal anesthesia of intermediate or short duration.[49–55]

Compared to an equipotent dose of long-acting spinal anesthetic, prilocaine showed a more rapid recovery and return of bladder function, associated with lower incidence of POUR (Evidence Ib).[23,29,36] Future trials are advocated to establish possible differences between prilocaine over other local anesthetics with similar favorable and safety profile, such as articaina and chloroprocaine.

The dose of prilocaine has to be related to the type of surgery, patient's characteristics, and local discharge criteria. Literature suggests a dose ranging between 40 and 60 mg for lower extremities and lower abdominal procedures lasting up to 90 min and 10 mg of 2% hyperbaric prilocaine for minor perianal surgery. Readiness for discharge occurs in about 4 h from spinal administration. In comparison with plain solutions, hyperbaricity remarkably accelerates the onset and offset times of intrathecal anesthesia.

Although the combination of prilocaine and fentanyl (20–25 μg) has been tested with the aim to improve the quality and extend the duration of the spinal block, pruritus and urinary retention are possible side effects which can delay home discharge.[29,36,37]

Limitations

Limitations of the present review are represented by the relatively small number of RCTs evaluating 2% hyperbaric prilocaine compared to any other local anesthetic, together with the heterogeneity of the doses used and the outcomes investigated, which does not permit a rigorous evidence-based evaluation of its advantages in outpatient spinal anesthesia.

Disclosure

The authors report no conflicts of interest in this work.

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