

Ambulatory surgery with chlorprocaine spinal anesthesia: a review

Daniela Ghisi
Stefano Bonarelli

Department of Anaesthesia and
Postoperative Intensive Care, Istituto
Ortopedico Rizzoli, Bologna, Italy

Abstract: Spinal anesthesia is a reliable and safe technique for procedures of the lower extremities. Nevertheless, some of its characteristics may limit its use for ambulatory surgery, including delayed ambulation, risk of urinary retention, and pain after block regression. The current availability of short-acting local anesthetics has renewed interest for this technique also in the context of short- and ultra-short procedures. Chlorprocaine (CP) is an amino-ester local anesthetic with a very short half-life. It was introduced and has been successfully used for spinal anesthesia since 1952. Sodium bisulfite was then added as a preservative after 1956. The drug was then abandoned in the 1980s for several reports of neurological deficits in patients receiving accidentally high doses of intrathecal CP during epidural labor analgesia. Animal studies have proven the safety of the preservative-free formulation, which has been extensively evaluated in volunteer studies as well as in clinical practice with a favorable profile in terms of both safety and efficacy. In comparison with bupivacaine, 2-chlorprocaine (2-CP) showed faster offset times to end of anesthesia, unassisted ambulation, and discharge from hospital. These findings suggest that 2-CP may be a suitable alternative to low doses of long-acting local anesthetics in ambulatory surgery. Its safety profile also suggests that 2-CP could be a valid substitute for intrathecal short- and intermediate-acting local anesthetics, such as lidocaine and mepivacaine – often causes of transient neurological symptoms. In this context, literature suggests a dose ranging between 30 and 60 mg of 2-CP for procedures lasting 60 minutes or less, while 10 mg is considered the no-effect dose. The present review describes recent evidence about 2-CP as an anesthetic agent for spinal anesthesia in ambulatory surgery.

Keywords: outpatient surgery, spinal anesthesia, 2-chlorprocaine

Introduction

In the last years, the number of surgical procedures performed on an ambulatory basis has increased worldwide:¹ between 50% and 70% of all surgeries are currently performed as outpatient procedures in North America alone.²

Spinal anesthesia is a safe and reliable technique for surgery of the lower abdomen and lower limbs.^{3,4} Nevertheless, some of its characteristics may limit its use for ambulatory surgery, including delayed ambulation, risk of urinary retention, and pain after block regression.⁵ The choice of the correct local anesthetic for spinal anesthesia is therefore crucial in the ambulatory setting: the ideal anesthetic should allow rapid onset and offset of its own effect for fast patient discharge with minimal side effects.⁶

In the past, the lack of the ideal spinal local anesthetic and the availability of fast-acting drugs such as remifentanyl and propofol have made general anesthesia the preferred choice for short outpatient procedures.^{7,8} To investigate the most suitable anesthetic technique for day surgery, Liu et al published a meta-analysis in 2005

Correspondence: Daniela Ghisi
Department of Anaesthesia and
Postoperative Intensive Care, Istituto
Ortopedico Rizzoli, via GC Pupilli,
1 – 40136 Bologna, Italy
Tel +39 340 265 3341
Fax +39 051 636 6356
Email ghisidan@hotmail.com

comparing regional and general anesthesia, including more than 1,300 patients.⁹ Regional anesthesia reduced pain scores and pain medication request in the post-anesthesia care unit. However, neither central neuraxial block nor peripheral nerve blocks decreased the overall ambulatory surgery unit time and both required longer induction time versus general anesthesia.⁹ However, the majority of studies included in the meta-analysis of Liu et al used long-acting or intermediate-acting local anesthetics for regional anesthesia, which may have delayed fulfillment of discharge criteria. Although low doses of long-acting local anesthetics such as bupivacaine, ropivacaine, and levobupivacaine are usually administered intrathecally, they are associated with significant risk of delays in hospital discharge and less reliability of block efficacy, onset, and spread.¹⁰

Short-acting local anesthetics may therefore represent a valid alternative in this setting. Lidocaine has been the anesthetic of choice for years in the context of outpatient procedures. Nevertheless, its use has been associated with a significant risk of transient neurological symptoms (TNS) and most anesthesiologists have therefore abandoned its use.^{11,12} Mepivacaine has been associated as well with transient neurological symptoms.¹²

The recent re-introduction of intrathecal articaïne, chloroprocaine (CP), and prilocaine may offer a solution in the ambulatory setting, with a slightly faster profile for CP.¹³

CP

CP is an amino-ester local anesthetic with a very short half-life.⁷ It was introduced and has been successfully used for spinal anesthesia since 1952.¹⁴ Sodium bisulfite was then added as a preservative after 1956 to the commercially available CP preparation, named Nesacaine-caudal and epidural. The drug was used as an epidural anesthetic for obstetric patients. In the early 1980s, several reports of neurologic deficits possibly associated with inadvertent intrathecal injection of large volumes of CP during labor analgesia were published.^{15–18}

Animal studies showed irreversible block after exposure of rabbit nerves to Nesacaine-caudal and epidural.¹⁹ Since a solution of 2 mg/mL sodium bisulfite and low pH without CP similarly led to irreversible block only at low pH, the preservative sodium bisulfite was often considered to be responsible for neural damage in an acidic environment.¹⁹ Nevertheless, in another study, rats developed more severe injuries after CP alone through intrathecal catheters than after CP with 2 mg/mL sodium bisulfite. Moreover, in the same study, the intrathecal administration of bisulfite alone was comparable to normal saline in rats.²⁰ Although the

reason of such divergent findings is not clear, a key role was probably played not only by different relative dosing of CP and bisulfite, but especially by the different susceptibility of different model systems to sulfur dioxide. The latter comes from the evidence that different levels/activity of sulfite oxidase (the protective enzyme that catalyzes the conversion of sulfites to the less toxic sulfates) exist in mammalian tissues.^{21,22}

All preservatives and antioxidants have been removed from two of the three currently available preparations of CP. In Europe, preservative-free 2-chloroprocaine (2-CP) is available as a 10 mg/mL solution (Ampres, Sintetica, Mendrisio, Switzerland), which was recently approved by the European Medicine Agency for intrathecal use, while it is currently available in the United States as a bisulfite-free solution (Nesacaine-MPF® from Astra Pharmaceuticals, Wilmington, DE, USA; generic CP from Bedford Pharmaceuticals, Bedford, OH, USA) as well as with preservative, although at a lower dose (generic CP from Abbott Laboratories, Abbott Park, IL, USA; sodium bisulfite =1.8 mg/mL versus 2.0 mg/mL of the original preparation). Due to availability of preservative-free solutions and since human studies have been conducted with the bisulfite-free CP, the bisulfite containing formulation is not indicated for intrathecal administration.

Spinal use of 2-CP

The use of preservative-free 2-CP for spinal anesthesia has been studied both in healthy volunteers and in patients.^{23–28} Main results of randomized controlled trials about the intrathecal use of CP published between 2004 and 2015 are reported in Table 1.

Besides volunteer studies, a chart review at the Virginia Mason Medical Center, published in 2004, evaluated the first 122 patients receiving spinal anesthesia with 2-CP: in terms of safety, the authors did not find any transient neurological symptom nor any sign of neurotoxicity.²⁹ Four patients required general anesthesia to complete surgery because of block resolution during the procedure, while two out of three patients with combined spinal/epidural anesthesia required epidural doses due to surgical length beyond the scheduled time. The 116 remaining patients tolerated the duration of surgery (≤ 60 minutes) with adequate surgical anesthesia and no complications.²⁹ This clinical retrospective analysis confirms also data about CP efficacy from volunteer studies.^{23–28} The majority of patients received a dose of 40 mg of 2-CP, which was also the most common dose in preclinical trials. Time intervals until ambulation for 30 and 40 mg of spinal 2-CP were consistent with previous volunteer studies, while

time to hospital discharge was slightly longer in surgical patients.²⁹

Another review from the same Institution was published in 2011 including 563 patients undergoing 601 ambulatory surgeries with spinal anesthetics between August 2004 and March 2006.³⁰ The 601 spinal anesthetics reviewed included 503 (84%) plain 2-CP and a lower percentage of hyperbaric lidocaine, hyperbaric bupivacaine, hyperbaric procaine, and plain mepivacaine, and safety and efficacy of CP was confirmed in the ambulatory setting in genitourinary procedures in the vast majority of cases, then orthopedic, general, and gynecologic surgeries. A preservative- and antioxidant-free formulation of 2% plain 2-CP (AstraZeneca plc, London, UK) was administered. Surgery lasted a mean time of 38±23 minutes. Primary failure of spinal block had an overall incidence of 1.2% due to inadequate spinal anesthesia and a secondary failure of 0.8% due to unanticipated surgical procedure length requiring conversion to general anesthesia.

Postoperative pain and urinary retention were the main reasons for delayed discharge from hospital in the study by Yoos and Kopacz.²⁹ Nevertheless, those five patients showing urinary retention underwent surgeries which increase the risk of urinary retention per se (trans-urethral resection of bladder tumor and perirectal surgery).³¹ Also in the review by Hejtmanek and Pollock,³⁰ urinary retention was confirmed as the most common post-anesthesia care unit side effect, although also in this case, 83% of patients underwent procedures characterized by a higher risk for urinary retention, such as cystoscopy, extracorporeal shock wave lithotripsy, peri-rectal or hernia surgery.³² Urinary retention is in fact a possible side effect of spinal block, especially with the use of bupivacaine and/or the addition of epinephrine to the local anesthetic.³² Despite an increased risk, Smith et al did not find any difference in the incidence of urinary retention with the addition of epinephrine to 2-CP in their volunteer studies, but 100% of volunteers reported vague, flulike symptoms with its use – a side effect not previously reported with the addition of epinephrine to other local anesthetics.²³ Authors hypothesized that these symptoms could be related to the acidic pH (3.5) of combined 2-CP and epinephrine and possibly to the trace amounts of bisulfite in the epinephrine vials. The use of epinephrine should therefore be avoided in combination with 2-CP for spinal injection.²³ Although currently debated, voiding has been traditionally considered a prerequisite for home discharge to avoid urinary retention especially after spinal anesthesia performed with long-acting local anesthetics.³³ However,

this can prolong hospital stay unnecessarily. Interestingly, it has been reported that if no surgery-related or underlying risk factors for urinary retention are present and short-acting local anesthetics are administered for neuraxial block the incidence of urinary retention is acceptably low.³⁴ Mulroy et al suggested a relaxation of the requirements for voiding before hospital discharge in outpatients receiving spinal block with short-duration drugs and undergoing surgical procedures at low risk of urinary retention, such as lower limb surgery.³⁵

Besides urinary retention, another possible complaint after spinal anesthesia is the occurrence of transient neurological symptoms, of which the lithotomy or flexed-knee positions (knee arthroscopy) are independent risk factors.³⁶ Nevertheless, in the survey by Yoos and Kopacz there are no case reports of TNS although 50% of patients were in the lithotomy or flexed-knee positions during surgery and 10% of cases had surgery in the prone jackknife position.²⁹ Also in the following retrospective analysis by Hejtmanek and Pollock, no case of TNS-like symptoms or neurotoxicity was reported and the preservative-free formulation of 2-CP has become the short-acting local anesthetic of choice at Virginia Mason Medical Center as a safe and effective alternative to lidocaine and procaine for short ambulatory procedures.³⁰

Many authors investigated the correct spinal dose of 2-CP to assure adequate efficacy and fast resolution of block in the ambulatory setting. Sell and Pitkanen tested four different doses of spinal 2-CP (35, 40, 45, and 50 mg) in a cohort of 64 patients scheduled for elective lower extremity procedures. The regression of sensory block and time to discharge were faster in the lower dose groups (35 and 40 mg), although the higher level blocked and time to complete block regression were comparable in all four groups.³⁷

In an attempt to find the minimum effective dose for intrathecal injection, Kopacz tested 10 and 20 mg of plain 2-CP.³⁸ The lower dose, 10 mg, should be considered the no-effect dose for spinal anesthesia, though it provided some transient motor weakness. Similarly, the 20 mg dose did not reliably produce dense motor block, even though it was able to produce a cephalad level of sensory anesthesia of at least L1 in all subjects.³⁸

Casati et al tested three different doses (30, 40, and 50 mg) for intrathecal administration in 45 patients undergoing elective lower limb procedures lasting less than 60 minutes and with a required dermatomeric level at T10.³⁹ As expected, spinal block resolution and time to recovery of ambulation results were dose-related. Casati et al included

Table 1 Main results of randomized controlled trials published about chloroprocaine between 2004 and 2015

Author, year of publication	Setting	Drug	Sensory block			
			Peak height	Tourniquet tolerance	Time until 2-dermatome regression	Resolution of sensory block
Kouri and Kopacz, 2004 ²⁷	8 healthy volunteers Age 35±6 years (clinical endpoints ^v and simulated discharge pathway)	40 mg plain chloroprocaine vs 40 mg 2% lidocaine	T8 (T5–I1) vs T8 (T6–I2)	46±6 min vs 38±24 min	57±14 min* vs 73±23 min	103±13 min* 126±16 min (at S2)
Smith et al, 2004 ²³	18 healthy volunteers Age 35±9 years (clinical endpoints ^v and simulated discharge pathway)	30, 45, and 60 mg hyperbaric chloroprocaine ± epinephrine	T8 (T10–T6), T4 (T11–C6), T1 (T8–C5)* T7 (L3–T2), T5 (T10–T1), T2 (T6–C5) (T6–C5) ^a	40±15 min, 72±21 min, 71±12 min* 37±11 min, 42±11 min, 62±10 min ^a	47±3 min, 52±17 min, 57±3 min 47±8 min, 45±3 min, 43±5 min ^a	153±25 min, 162±33 min, 148±29 min* 98±20 min, 116±15 min, 132±23 min ^a
Vath and Kopacz, 2004 ²⁴	8 healthy volunteers Age 37±13 years (clinical endpoints ^v and simulated discharge pathway)	40 mg chloroprocaine ±20 µg fentanyl	T5 (T7–T3)* vs T8 (L1–T4)	51±8 min* vs 34±14 min	48±8 min vs 45±16 min	104±7 min* vs 95±9 min
Warren and Kopacz, 2004 ²⁵	8 healthy volunteers Age 21–48 years (clinical endpoints ^v and simulated discharge pathway)	40 mg chloroprocaine with 0.25 mL 10% dextrose or 0.25 mL saline	T3 (T7–C6) vs T4 (T7–C7)	45±7 min vs 42±11 min	40±10 min vs 47±8 min	95±8 min vs 96±9 min
Kopacz, 2005 ³⁸	8 healthy volunteers Age 40±11 years (clinical endpoints ^v and simulated discharge pathway)	10 mg vs 20 mg chloroprocaine	L1 (T8–L4) vs T9 (T4–L1)	7±6 min vs 22±9 min	40±18 min vs 37±12 min	49±10 min* vs 72±11 min
Davis and Kopacz, 2005 ²⁶	8 healthy volunteers Age 27–60 years (clinical endpoints ^v and simulated discharge pathway)	30 mg chloroprocaine ±15 µg clonidine	T8 (T4–T11) vs T8 (T6–L2)	46±11 min vs 33±12 min	50±9 min vs 50±22 min	131±15 min* vs 99±18 min
Yoos and Kopacz, 2005 ²⁹	122 patients Age 55±16 years Variety of surgical procedures	Chloroprocaine 20–60 mg ±10–20 µg fentanyl (rarely dextrose or water)	Peak T6–T8. More than T10 in all patients	NA	NA	NA
Yoos and Kopacz, 2005 ²⁹	8 healthy volunteers Age 38±7 years (clinical endpoints ^v and simulated discharge pathway)	Chloroprocaine 40 mg vs bupivacaine 7.5 mg	T7 (T3–T10) vs T9 (T4–L1)	NA	45±20 min* vs 74±20 min	113±14 min* vs 191±30 min
Gonter and Kopacz, 2005 ²⁸	Healthy volunteers Age 42±11 years (clinical endpoints ^v and simulated discharge pathway)	Chloroprocaine 30 mg vs procaine 80 mg	T9 (T6–T12) vs T6 (T4–T8)	37±16 min vs 49±17 min	51±17 min vs 53±10 min	103±12 min* vs 151±26 min
Casati et al, 2006 ³⁹	45 ASA I–II outpatients Age 59±13, 56±14, 48±16 years ^b Lower limb surgery	Chloroprocaine 30, 40, and 50 mg	NA	NA	NA	60 (41–98) min,* 85 (46–141) min, 97 (60–169) min ^b

Motor block		Discharge time		Complications
Time until recovery at abdomen	Time until recovery – Bromage Scale	Ambulation	Micturition	Complications
71±18 min vs 60±53 min	79±15 min vs 90±14 min	104±12 min* vs 134±14 min	104±12 min* vs 134±14 min	TNS in 7 out of 8 patients with lidocaine No TNS with chloroprocaine
60±65 min, 88±43 min, 80±26 min* 43±26 min, 56±9 min, 78±16 min ^a	90±30 min, 131±46 min, 120±30 min* 72±12 min, 88±15 min, 100±13 min ^a	158±33 min, 162±33 min, 151±33 min* 100±20 min, 119±15 min, 133±20 min ^a	167±47 min, 161±33 min, 164±24 min* 100±21 min, 132±19 min, 141±21 min ^a	Nonspecific flu-like symptoms, radiating back pain (2 pt), non-radiating low back ache (4 pt) after 2-CP and epinephrine non-radiating low back pain (1 pt) after 2-CP
61±11 min vs 49±10 min	81±16 min* vs 67±13 min	104±7 min* vs 95±9 min	104±7 min* vs 95±9 min	Itching (no treatment required) when fentanyl was used
64±12 min vs 60±19 min	80±14 min vs 81±15 min	96±7 min vs 96±9 min	101±7 min vs 96±9 min	Greater residual bladder volumes in the dextrose group
NA	16±15 min* vs 48±7 min	44±19 min* vs 73±9 min	50±10 min* vs 73±9 min	No TNS
NA	79±19 min* vs 65±13 min	131±15 min* vs 99±18 min	131±15 min* vs 99±18 min	No TNS
NA	NA	155±35 min	207.9±69.4 min (discharge)	11 patients complained of nausea in the PACU No TNS
NA	81±15 min* vs 138±24 min [¶]	113±14 min* vs 191±30 min	113±14 min* vs 191±32 min	No TNS
NA	54±23 min vs 55±44 min	103±12 min* vs 151±26 min	103±12 min* vs 156±23 min	Pruritus in 1 patient and dysphoria in 1 patient (both in the procaine group)
NA	NA	85 (45–198) min,* 180 (72–281) min, 185 (90–355) min ^b	182 (120–267) min, 198 (123–271) min, 203 (102–394) min ^b	No TNS

(Continued)

Table 1 (Continued)

Author, year of publication	Setting	Drug	Sensory block			
			Peak height	Tourniquet tolerance	Time until 2-dermatome regression	Resolution of sensory block
Casati et al, 2007 ⁴⁰	30 ASA patients Age 18–70 years Knee arthroscopy	Chloroprocaine 50 mg vs lidocaine 50 mg	NA	NA	NA	120 (80–175) min* vs 95 (68–170) min
Sell et al, 2008 ³⁷	64 ASA I–III patients Age 18–80 years Lower limb surgery	Chloroprocaine 35, 40, 45, and 50 mg	T9 in all groups	NA	NA	111 (96–126) min,* 108 (95–121) min,* 128 (116–138) min, 134 (123–145) min ^c
Lacasse et al, 2011 ⁴⁴	106 ASA I–III patients Age >18 years Short ambulatory procedures	Chloroprocaine 40 mg vs bupivacaine 7.5 mg	T7 (T1–T10) vs T7 (T1–T11)	NA	50±18 min* vs 75±37 min	146±38 min* vs 329±82 min
Forster et al, 2011 ¹³	70 ASA I–II patients Age ≤65 years Day-case knee arthroscopy	Chloroprocaine 40 mg vs articaine 60 mg	T10 (T12–T6) vs T10 (T11–T5)	NA	60 (45–75) min vs 60 (45–75) min	105 (105–135) min* vs 165 (135–180) min
Vaghadia et al, 2012 ⁴¹	40 ASA I–III patients Age 59–78 years TURP	Chloroprocaine 40 mg + 12.5 µg fentanyl vs 35 mg lidocaine + 12.5 µg fentanyl	T8 in both groups	NA	NA	155±55 min vs 163±37 min
Forster et al, 2013 ⁴³	36 ASA I–III patients Age 18–70 years Day-case knee surgery	Chloroprocaine 40 mg vs articaine 40 mg	T8 (T10–T7) vs T8 (T12–T6)	NA	60 (45–60) min* vs 75 (49–75) min	105 (90–124) min* vs 135 (109–176) min
Breebart et al, 2014 ⁴²	100 ASA I–II patients Age, mean (SD): 44 (12); 46 (14); 43 (12); 51 (12) years ^d Knee arthroscopy	Lidocaine 60 mg ±500 mL iv preload (lidocaine+; lidocaine–)Chloroprocaine 40 mg ±500 mL iv preload (CP+; CP–)	T5, T5, T7, T7 ^d	NA	NA	140 (46) min, [#] 129 (37) min, [#] 92 (25) min, ^{##} 86 (21) min, ^{##,d}
Camponovo et al, 2014 ⁴⁵	130 ASA I–II patients Age 18–80 years Lower abdominal or lower limb procedures (T10 level required)	Chloroprocaine 50 mg vs bupivacaine 10 mg	T10 (T10–T3) vs T10 (T10–T2)	NA	NA	105 (60–194) min* vs 225 (130–442) min

Notes: Data are shown as mean ± standard deviation or median (25th–75th percentiles), unless stated otherwise. *Significant versus other treatment/group. [#]Regression to L2. [†]Gastrocnemius dynamometry (90% of baseline) (minutes). ^ΔTime to hospital discharge. ^aThe first three rows of data are results for hyperbaric chloroprocaine 30, 45 and 60 mg with epinephrine, and the next three rows of data are results for 30, 45 and 60 mg without epinephrine. ^bThe three rows or items of data are the results for chloroprocaine 30, 40, and 50 mg, respectively. ^cThe four rows of data are the results for chloroprocaine 35, 40, 45, and 50 mg, respectively. ^dThe four rows or items of data are the results for lidocaine+, lidocaine–, CP+, and CP–, respectively.

Abbreviations: 2-CP, 2-chloroprocaine; ASA, American Society of Anesthesiologists; CP, chloroprocaine; CP+, chloroprocaine with iv preload; CP–, chloroprocaine without iv preload; iv, intravenous; min, minutes; lidocaine+, lidocaine with iv preload; lidocaine–, lidocaine without iv preload; NA, not available; PACU, post-anesthesia care unit; PDPH, post-dural puncture headache; POD, postoperative day; PONV, postoperative nausea and vomiting; pt, patient(s); TNS, transient neurological symptoms; TURP, transurethral resection of the prostate.

patients undergoing procedures lasting between 45 and 60 minutes, finding that 33% of patients in the 30 mg group required intraoperative analgesic supplementation as a result of insufficient analgesia. The authors concluded that the 30 mg dose may not be suitable for lower limb procedures lasting ≤60 minutes.³⁹

Yoos and Kopacz found instead an increasing tendency toward the administration of the lowest dose of 30 mg of 2-CP in their ambulatory setting, and a decrease in the addition of fentanyl among their anesthesiologists, indicating that the correct patient and surgery selections allow a successful use also of the 30 mg dose.²⁹

Motor block		Discharge time		Complications
Time until recovery at abdomen	Time until recovery – Bromage Scale	Ambulation	Micturition	Complications
NA	100 (60–140) min* vs 60 (45–120) min	152 (100–185) min* vs 103 (70–191) min	190 (148–340) min vs 180 (100–354) min	TNS in 33% of patients in the lidocaine group. No TNS with chloroprocaine
NA	106 (91–121) min, 100 (99–123) min, 111 (99–123) min, 119 (102–137) min ^c	117 (103–131) min,* 116 (103–130) min,* 127 (106–148) min, 144 (128–161) min ^c	123 (108–138) min,* 122 (109–135) min,* 137 (124–149) min, 165 (141–189) min ^c	No TNS
NA	76±25 min* vs 119±93 min	225±56 min* vs 265±65 min	271±96 min* vs 338±99 min	1 post-dural puncture headache per group, 1 TNS per group, 45% back ache after 2-CP and 38% after bupivacaine
NA	75 (60/90) min* vs 135 (105/150) min	318±74.2 min vs 392±93.2 min [^]	204±61.8 min vs 219±71.6 min	No TNS
81±41 min 71±41 min	117±36 min 120±35 min	NA	NA	4 patients developed TNS with lidocaine 1 patient developed cauda equina syndrome after chloroprocaine fully recovered after some weeks
NA	75 (71/90) min* vs 105 (94/120) min	NA	171 (163/197) min vs 236 (152/279) min	5 patients had PONV in both groups on first POD 1 patient had PONV after articaine vs 4 patients after chloroprocaine on POD 7 2 patients after articaine vs 3 after chloroprocaine had non-PDPH on POD 1 3 patients after articaine vs 1 patient after chloroprocaine had non-PDPH on POD 7 1 patient showed TNS after articaine on POD 1
NA	95 (26) min, [#] 94 (10) min, [#] 65 (20) min, ^{*,*} 62 (20) min, ^{*,*,d}	NA	210 (55) min, 205 (58) min, 161 (36) min,* 175 (51) min ^d	1 patient complained of TNS after lidocaine
NA	100 (40–194) min* vs 210 (120–415) min	142.5 (86–454) min* vs 290.5 (190–490) min	NA	1 patient experienced foot cramps after bupivacaine 1 patient reported non-PDPH after bupivacaine 1 patient reported injection site pain after bupivacaine No TNS was reported

2-CP versus other fast-acting local anesthetics

In the retrospective review by Hejtmanek and Pollock,³⁰ 2-CP showed a faster profile than lidocaine in terms of time from injection to ambulation and time from injection to hospital discharge with a comparable incidence of urinary retention.

The comparison with lidocaine, as well as with other short-acting local anesthetics, has been extensively evaluated in literature. Kouri and Kopacz compared intrathecal injection of 40 mg 2% lidocaine with 40 mg 2% 2-CP in eight healthy volunteers and demonstrated a faster profile for 2-CP, demonstrating shorter resolution time of sensory block and

a significantly shorter time to complete block regression and voiding.²⁷ Consistently with these volunteer data, Casati et al found a faster recovery profile of sensory and motor blocks and faster time-to-ambulation after 2-CP than after an equal dose of lidocaine in 30 patients undergoing knee arthroscopy. No significant differences were noted in times for hospital discharge due to comparable times to spontaneous voiding, which was required as a criterion for patients' discharge.⁴⁰

Also Vaghadia et al compared lidocaine and 2-CP in combination with fentanyl, to provide selective spinal anesthesia for outpatient transurethral resection of the prostate. The authors did not find any statistical difference between the two groups with respect to onset and offset of spinal block variables. The authors reported four cases of transient neurological symptoms after lidocaine and one case of cauda andom-like syndrome after CP in a 66-year old patient, who developed symptoms within 24 hours after an uneventful L3-L4 spinal anesthesia with a 25 G needle, persisting for several weeks. The patient complained of numbness in both buttocks extending down the posterior thighs to both feet, thigh weakness, stabbing pain in his anterior legs bilaterally requiring treatment with oral oxycodone, and urinary retention. Nevertheless, the patient recovered after some weeks.⁴¹

A more recent study by Breebart et al, randomized 100 patients undergoing day-case arthroscopy to receive either lidocaine 60 mg or CP 40 mg intrathecally with or without a 500 mL pre-load of crystalloid. The authors found no differences in voiding time within the CP or lidocaine groups, although discharge and micturition was faster with CP than lidocaine. When looking at subgroups, only the CP group receiving pre-load was discharged faster than both the lidocaine groups and more serious micturition problems (requiring single in and out bladder evacuation) occurred in the lidocaine group with pre-load compared with both CP groups, demonstrating a more favorable profile for CP in the ambulatory setting.⁴²

CP 30 mg was also compared to another fast-acting local anesthetic, procaine 80 mg, showing similar surgical efficacy but significantly shorter sensory block and discharge times.²⁸

Förster et al compared articaine 40 mg to CP 40 mg in 36 patients scheduled for day-case knee arthroscopy. The authors found comparable onset and maximal spread of spinal anesthesia, while offset was significantly slower with articaine than CP.⁴³

CP versus bupivacaine

2-CP has been compared to bupivacaine in the studies by Yoos and Kopacz³⁵ and Lacasse et al.⁴⁴ In the first study, 40

mg of 2-CP was compared with 7.5 mg of bupivacaine in a double-blind, randomized, crossover, volunteer study in terms of pinprick anesthesia, motor strength, tolerance to tourniquet and electrical stimulation, and simulated discharge criteria.³⁷ Lacasse et al compared 7.5 mg of hyperbaric bupivacaine 0.75% to 40 mg of 2-CP 2% in 106 patients.⁴⁴ The authors in both studies found significantly longer discharge times with low-dose bupivacaine than with 2-CP. All offset variables showed a faster resolution of the spinal block after 2-CP, including time for two-segment regression, time for regression to L1, time for complete regression to S2, duration of motor blockade, time-to-ambulation as well as time to first analgesic requirement. Lacasse et al reported one case of TNS after spinal 2-CP and one case after spinal bupivacaine, both identified at the 24-hour follow-up phone call. Symptoms were defined as pain or dysesthesia in the legs and/or buttocks in the first 24 hours after recovery in two female patients aged 50 to 60 years old who underwent transobturator tension-free urethral suspension in the lithotomy position. As claimed by the authors, differential diagnosis includes the well-described neuropathies known to be associated with the lithotomy position as well as surgical trauma due to entrapment of the obturator nerve during placement of the sling. The authors could therefore not be conclusive about the diagnosis of TNS.⁴⁴ Patients receiving intrathecal 2-CP demonstrated faster times to micturition and times between first try and successful voiding. Camponovo et al also performed a clinical study demonstrating that spinal anesthesia performed with 50 mg of plain 1% 2-CP provides adequate spinal anesthesia for lower abdominal and lower limb outpatient procedures lasting less than 40 minutes, with faster recovery from anesthesia and eligibility for home discharge in comparison with 10 mg of plain 0.5% bupivacaine.⁴⁵ The authors found onset time to be almost the same with 1% 2-CP 50 mg and 10 mg bupivacaine 0.5% and confirmed faster offset times after 2-CP spinal anesthesia.⁴⁵

Conclusion

The availability of reliable and safe short-acting local anesthetics has recently renewed interest in spinal technique for outpatient surgery, offering an alternative to general anesthesia.

Intrathecal 1% or 2% 2-CP represents an interesting alternative to lidocaine for surgical blocks and short or ultra-short surgical procedures. When compared with spinal bupivacaine, it resulted in a significantly faster offset of sensory and motor blocks with similar onset time. The safety of intrathecal use of the preservative-free 2-CP formulation is currently sustained both by volunteer and clinical studies. Literature suggests a dose ranging between

30 and 60 mg for procedures lasting 60 minutes or less, while 10 mg is considered the no-effect dose. Further investigations are necessary to address the adequacy of the lower recommended dose of 30 mg in ultra-short procedures lasting 40 minutes of the lower extremities (required dermatome level at T12).

Disclosure

Stefano Bonarelli and Daniela Ghisi report no conflicts of interest in this work.

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