ORIGINAL ARTICLE

Randomised controlled trial of spinal anaesthesia with bupivacaine or 2-chloroprocaine during caesarean section

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The authors have nothing to disclose.

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Background: Neuraxial anaesthesia is the desired method for Caesarean section. Bupivacaine is a well-known local anaesthetic. It has a long duration of action and can cause unpredictable levels of anaesthesia with subsequent prolonged discharge time. 2-Chloroprocaine has a rapid onset of action, producing an excellent sensory and motor block and has a rapid hydrolysis in the bloodstream by pseudocholinesterase. We compared bupivacaine and 2-chloroprocaine for spinal anaesthesia during Caesarean section. The primary endpoint was the earliest reversal sign of the motor block.

Methods: Sixty ASAI/II patients, planned for elective singleton Caesarean section, were equally randomised to three groups. All patients received a combined spinal–epidural anaesthesia. The first group received 2-chloroprocaine (40 mg) without sufentanil, the second group received 2-chloroprocaine (40 mg) with sufentanil (1 μg) and the third group received hyperbaric bupivacaine (7.5 mg) with sufentanil (1 μg) as a spinal anaesthetic. Motor and sensory blockade were assessed at specific time points.

Results: There was no difference between the three groups regarding the time to regression of the motor block. However, at 5 min post spinal injection, the level of sensory block was higher for both groups with 2-chloroprocaine, in comparison with the bupivacaine group.

Conclusion: 2-Chloroprocaine can be used for low risk Caesarean section in healthy parturients. There is no difference in time to motor block resolution compared to bupivacaine.
Motor recovery seems more predictable for 2-chloroprocaine and may be beneficial for the breastfeeding initiation.

Editorial comment: what this article tells us
This study tells us that while spinal anaesthesia with 2-chloroprocaine for low-risk Caesarean section has a fast onset for sensory block, it also has a predictable and relatively rapid motor block recovery time.

Neuraxial anaesthesia in combination with spinal–epidural anaesthesia (CSE) is the gold standard method for Caesarean section (CS). It is safe to the parturient and newborn compared to general anaesthesia and has reportedly low maternal mortality.[1,2] In addition, parturients remain awake during surgery thus experiencing the birth of their baby. The spinal component

provides rapid onset of anaesthesia while the epidural catheter allows administration of local anaesthetics during and after surgery to maintain analgesia.[3]

Bupivacaine is a well-known amide-type local anaesthetic, which has been used as a spinal anaesthetic since the 1960s. It has a long duration of action and can cause unpredictable levels of anaesthesia, which are dose dependent with subsequent prolonged discharge time.[4–6] Even with small doses of bupivacaine, disadvantages have been reported. These include inadequate blockade height for the surgical procedure, urinary retention, prolonged block resolution, which leads to delayed discharge from the post-anaesthesia care unit (PACU).[4] Our current hospital policy states that parturients should remain in PACU until complete reversal of the motor block. During this time the newborn remains on the maternal ward. This has implications and potential delays with the first breastfeeding session.[7] Despite drawbacks, bupivacaine remains widely in use for CS.[8,9]

Chloroprocaine (2-chloroprocaine, 2-CP) is an ester-type local anaesthetic that was introduced into clinical practice in 1952 and used successfully in 214 patients as a spinal anaesthetic.[10] 2-CP has a rapid onset of action, producing an excellent sensory and motor block and has a rapid hydrolysis in the bloodstream by pseudocholinesterase. These characteristics account for its early popularity, particularly in obstetrics. 2-CP has a short plasma half-life minimising possible systemic toxicity for the mother and foetus. Concerns in the 1980s regarding the safety and potential neurotoxicity of 2-CP were highlighted by several reports of high dose intrathecal administration of 2-CP.[11,12] These complications were associated with the acidic solution and in particular the preservative bisulfite.[13] Since 1996, 2-CP was manufactured without additives and the pH of the solution improved. Multiple studies with healthy volunteers showed good results without complications. They found a predictable time of onset, blockade height and time to complete regression.[6,14,15]

Recently, 2-CP has been marketed solely for spinal use. Contemporary evidence on the current form of 2-CP is limited in relation to spinal anaesthesia for CS.

We tested the null hypothesis in a prospective single blinded manner that the earliest regression of the motor block between the three groups was not different. Also, the effectiveness and characteristics of sensory blockade, the differences regarding maternal blood pressure and heart rate, neonatal effects and side effects have been assessed.

Methods

After Ethical Committee approval (Ethical Committee Clinical Trials, University Hospital Brussels 2013/186) and approval by the Belgian Federal Agency for Medicines and Health Products (FAMHP – 582184), we conducted a prospective controlled trial. (EudraCT 2013-002815-88)

Patients

After signed informed consent, all in-term patients (≥ 37 weeks) with American Society of Anaesthesiologists (ASA) physical status I or II, planned for a CS were consecutively included to participate to this blinded randomised trial. Included were all women with an uncomplicated, singleton pregnancy. Patients were aged between 18 and 40 years. Exclusion criteria included ASA physical status III and IV, urgent and emergent CS, twin and multiple pregnancy, gestational age less than 37 weeks, body mass index (weight/height^2) (BMI) > 35 kg/m^2 (before pregnancy), maternal height < 150 cm, foetus with known or suggested congenital malformations, known allergy for the used local anaesthetics and (pre)eclampsia.

Study protocol

The recommendations by the Consolidated Standards of Reporting Trials (CONSORT) for reporting a randomised, controlled clinical trial were followed. All patients were equally randomised in three groups. Numbered sealed envelopes, from 1 (first patient) to 60 (last patient), following a computer-generated list, were used to reveal group allocation just before the procedure. Each envelope contained a card showing the relevant group. The anaesthetist, who also was the assessor, opened the envelope

just before starting the procedure. The first group received 2-CP (40 mg) without sufentanil (group C), the second group received 2-CP (40 mg) with sufentanil (1 μg) (group C+S) and the third group received hyperbaric bupivacaine (9 mg) with sufentanil (1 μg) (group B+S). Single blinding was achieved by not revealing group allocation to the patients.

Monitoring

Before initiation of spinal block, the following parameters were measured and recorded: maternal age, length, weight before pregnancy, weight at the end of pregnancy, medical history and pregnancy term. Furthermore, maternal blood pressure, heart rate and oxygen saturation were noted before initiation of anaesthesia and were referred as baseline values. All patients received a fluid loading of 500 ml colloid solution (Volulyte®) with 200 μg phenylephrine, 30 min before the start of the procedure[16], which is standard care in our institution.

The CSE technique is summarised: the epidural space is identified in a seated patient, at level L4-L5 or L4-L3 interspace with an 18-gauge Tuohy needle using the "loss of resistance to saline" technique. A 27-gauge pencil-point spinal needle perforates the dura via the Tuohy needle. When the cerebrospinal fluid is free flowing, the study medication, defined following subset allocation, was injected. Afterwards, a 20-gauge epidural catheter was positioned 4 cm in the epidural space. If analgesia was insufficient during the surgery, a top-up dose of 10 ml ropivacaine 7.5mg/ml was given after testing the epidural catheter.

After this procedure, the patient was installed in the left lateral tilt on the operating table. She received a bladder catheter and a non-rebreathing mask with 10 l/min oxygen until birth of the baby.

All observations were assessed by the study anaesthetist. Motor and sensory block were tested 5 min after intrathecal injection (T0) (and thus before surgery). The 5-min interval was chosen as this time interval is clinically utilised in our daily clinical practice. Motor block was assessed by a modified Bromage scale from 1 to 6: 1 = no motor block, 2 = weak hip flexion, 3 = weak knee extension, 4 = week knee flexion, 5 = weak dorsiflexion of feet, 6 = weak plantar flexion of feet. Sensory block was assessed by loss of cold sensation. The currently recommended level of sensory block for CS is T5–T4.[17]

Pain was assessed at 5, 10, 20, 30, 40, 50 and 60 min after injection, by using a VAS (Visual Analogue Scale). Maternal blood pressure, heart rate, oxygen saturation, presence of nausea and vomiting were recorded at the same time points as pain was assessed. Maternal hypotension was registered and defined as a drop of systolic blood pressure of more than 20% of the baseline value that was measured before initiation of the procedure. In this case, a bolus of 100 μg phenylephrine was given till blood pressure returned within 20% of starting value limits.

Time of birth, neonatal outcome (Apgar score) and admission to NICU were recorded as well as umbilical venous and arterial blood gasses.

End of surgery time was recorded and motor/sensory block were tested again in those patients who did not receive a top up dose through the epidural catheter.

After surgery and after relief of motor block (Bromage scale = 1), the epidural catheter was tested and a patient controlled epidural pain pump (PCEA) was started to relief post-operative pain.

Statistical analysis

Being unaware of any previous comparative studies between 2-CP and bupivacaine in this setting of CS, we calculated the number of patients to be included from an initial subset of 12 patients, divided over the three groups. A sample size of 18 patients per group was required to detect a 15 min difference in regression of motor blockade using the Mann–Whitney *U*-test with a power of 80% and a two-tailed risk of 5%.

Continuous variables were expressed as mean [standard deviation (SD)]. Categorical variables are presented as absolute values. For analysis, the spinal segments from T12 to T1 were numbered from 12 to 1 and these were treated as ordinal data.

For comparison between patient groups, analysis of variance was used as well as an independent sample *t*-test when appropriate.

Discontinuous data were analysed by a Fisher's exact test. The threshold for statistical significance was set at 5%.

All statistical analyses were performed using SPSS 22 for MAC (SPSS Inc., Chicago, IL, USA).

Results

A total of 60 patients were screened and randomised consecutively from September to December 2013. Two patients were not randomised because of withdrawal of informed consent. From the 58 remaining patients, two were excluded for analysis because of failed spinal block (one belonging to the group C+S and the group B+S, respectively). Before starting surgery, sensory block was absent, implying an epidural loading dose. Finally, 56 patients were considered in the analysis. The CONSORT flow diagram of the study design is shown in Fig. 1.

Demographic data of all subjects including age, weight, height, BMI, gestational age, ASA status, CS in history and gestational diabetes mellitus were recorded from the medical file before the start of the procedure and are presented in Table 1. No differences were found between the three groups.

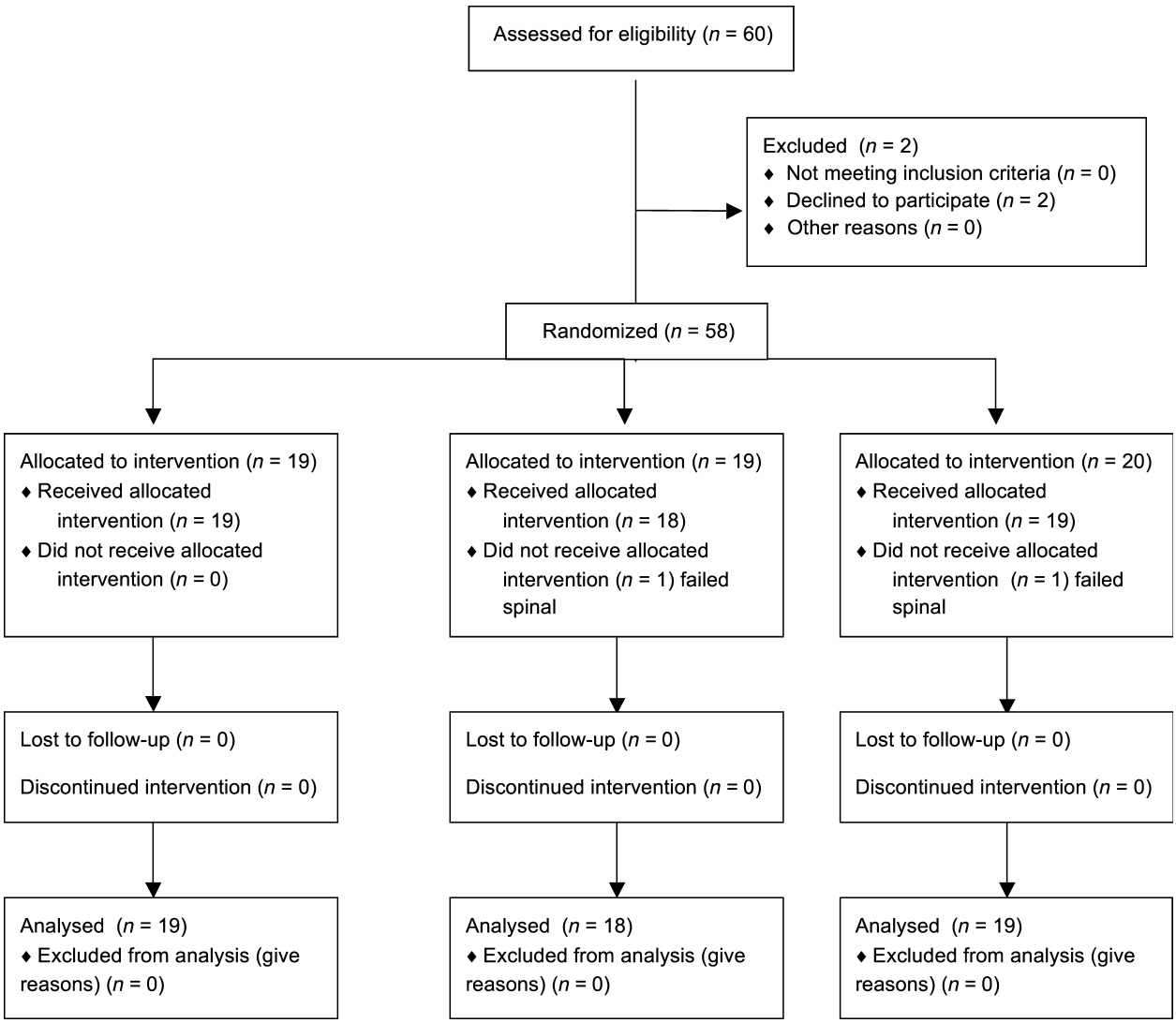

Fig. 1. Consort flow diagram.

The time for regression of motor block (T reg), main outcome variable, was similar in all three groups. However, there was a tendency for a wider variability and less predictability of results in the B+S group, with a total range of 96 min (54–150 min) vs. 56 min (57–113 min) for the C group and 73 min (41–114 min) for the C+S group (Fig. 2). The 95% confidence intervals for the respective subsets were: group C (70–85 min), group C+S (67–87 min) and group B+S (75–102 min).

Secondary results are shown in Table 2. The level of sensory block (SB) was higher for both groups with 2-CP, 5 min after spinal injection in comparison with the B+S group ($P < 0.01$). We compared the occurrence of a sensory block at level T4 and T5 between the three groups by using a Fisher's exact test. For both levels, the difference between B+S and C or B+S and C+S were statistically significant ($P < 0.01$).

Two patients reported a VAS of 3 after 20 min, respectively in the C+S and B+S group. After 40 min, seven patients reported a VAS above 1. Two of those patients belong to the C group and reported the highest VAS scores of 4 and 5. One in the same group described a VAS of 5, 50 min after injection. VAS scores were lower in both sufentanil groups.

Some patients suffered from hypotension during the procedure. There was no significant difference between the three groups. Several patients suffered from nausea and vomiting but there was no significant difference between subsets.

APGAR scores and umbilical blood gasses (arterial and venous pH) were measured for all babies and were not significantly different between groups. One newborn was admitted to the neonatal intensive care unit, within 24 h after birth (APGAR 10/10/10), because of respiratory distress, which improved after a small period of CPAP therapy.

Table 1 Demographic data of included patients.

	Group C (n = 19)	Group C + S (n = 18)	Group B + S (n = 19)
Age (years)	32.1 ± 4.9	33.4 ± 4.9	30.6 ± 5.0
Height (cm)	168 ± 7	165 ± 5	165 ± 7
Weight (kg)	69.6 ± 7.9	67.0 ± 9.2	68.1 ± 16.7
BMI (kg/m^2)	24.8 ± 3.1	24.6 ± 3.4	24.9 ± 5.8
Gestational age (weeks)	38.8 ± 1.1	38.6 ± 0.9	38.5 ± 1.2
ASA score I/II (n)	16/3	14/4	18/1
Repeat Caesarean section (n)	13	12	9
Gestational DM (n)	2	3	1

Group C, 2-chloroprocaine; group C+S, 2-chloroprocaine + sufentanil; group B + S, bupivacaine + sufentanil; ASA, American Society of Anesthesiologists; BMI, body mass index (weight(kg)/height(m)^2); gestational DM, gestational diabetes mellitus; n, number of patients. Values are presented as mean ± SD.

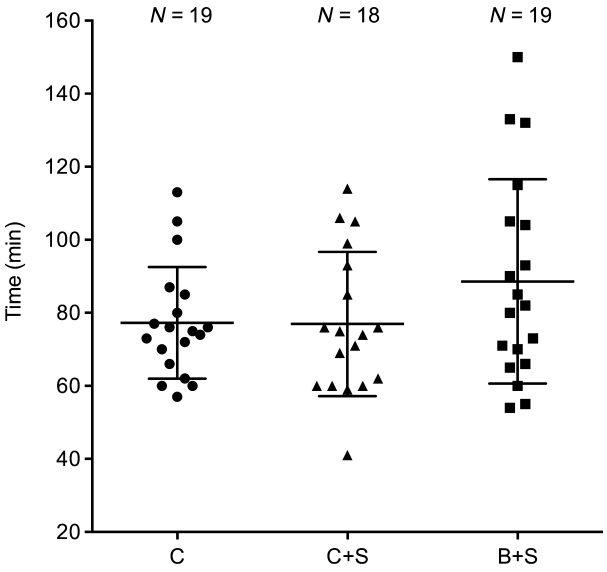

Fig. 2. Time to achieve resolution of motor block in women receiving one of three anaesthetic drugs. C, 2-chloroprocaine; C+S, 2-chloroprocaine + sufentanil; B+S, bupivacaine + sufentanil. Middle horizontal line represents mean value, with standard deviations (upper and lower horizontal lines).

Discussion

2-CP is frequently used as spinal anaesthetic for ambulatory surgery.[18,19] To the best of our knowledge this is the first study evaluating the value of 2-CP during CS.

This study demonstrates the following, in women undergoing an elective CS:

- 2-CP can be used for low-risk CS
- Time to regression of motor block with 2-CP was comparable with bupivacaine induced motor block, albeit the regression in the latter appeared to be less predictable.

Table 2 Comparison between the three groups for: time of resolution of motor block, sensory block 5 min after spinal injection, surgery time, occurrence rate of hypotension and nausea. For comparison between groups, analysis of variance was used (*P* value) as well as an independent sample *t*-test when appropriate*,†.

	Group C (*n* = 19)	Group C + S (*n* = 18)	Group B + S (*n* = 19)	*P* value
T reg (min)	77 ± 15	77 ± 20	89 ± 28	0.18
SB (median, range)	T4 (T4–T7)	T4 (T3–T6)	T7 (T4–T10)	< 0.01*,†
T sur (min)	38 ± 7	37 ± 5	42 ± 8	0.06
Hypotension 5′: n (%)	4 (21%)	2 (11%)	3 (16%)	0.63
Hypotension 10′: n (%)	8 (42%)	8 (44%)	8 (42%)	0.95
Hypotension 20′: n (%)	3 (16%)	4 (22%)	3 (16%)	0.53
Hypotension 30′: n (%)	8 (42%)	2 (11%)	4 (21%)	0.70
Nausea: n (%)	5 (26%)	4 (22%)	3 (16%)	0.73

Group C, 2-chloroprocaine; group C+S, 2-chloroprocaine + sufentanil; group B+S, bupivacaine + sufentanil; Hypotension 5′-10′-20′-30′, hypotension respectively 5, 10, 20 and 30 min after spinal injection; Nausea, occurrence of nausea during procedure; SB, sensory block 5 min after spinal injection; T reg, time of regression of motor block; T sur, surgery time. Times are presented as minutes rounded off to the nearest whole minute (mean ± SD). Other values are shown as number of patients (%). Statistical significance if $P < 0.05$. *Independent samples *t*-test between B+S and 2-CP+S: $P < 0.01$. †Independent samples *t*-test between B+S and 2-CP: $P < 0.01$.

- Haemodynamic stability, neonatal outcome and side effects were comparable for both anaesthetics.

Motor block regression is comparable in both groups although the spread of data was much larger in the bupivacaine group. This suggests that the motor block regression for bupivacaine is less predictable compared to 2-CP. Yoos et al. compared 2-CP 40 mg with bupivacaine 7.5 mg. They concluded that 2-CP has a significantly faster resolution of block and return to ambulation compared with bupivacaine.[6] Different studies confirm these findings.[4,5,20,21]

The currently recommended level of sensory block required for CS is T5–T4. However, there are no clear recommendations about the assessment of the sensory block.[17] Different studies have shown that the mean time to achieve spinal block up to T5–T4 with bupivacaine varies between 4 and 12 min.[8,22] All these studies use different protocols, hampering correct comparability. In the present study 54% of the patients with 2-CP had a sensory block above T4 and 84% above T5, 5 min after spinal injection, compared to only 5% and 16% respectively in the bupivacaine group. This suggests that 2-CP could be very attractive for urgent CS, where time to incision should be as short as possible.

Three patients in the 2-CP group reported a VAS above 3 after 40 and 50 min respectively. This could be explained by the pain that occurs on the moment of internalisation of the uterus and peritoneal closure.[23] Repair of the uterine incision during CS is always performed by uterine externalisation in our institution. Unfortunately specific points in the surgical procedure and the corresponding patient experiences were not recorded. Therefore, we cannot make any conclusion about this topic. The addition of opioids showed lower VAS scores, both in combination with 2-CP and bupivacaine. Different studies have shown that opioids can improve the quality of analgesia, extend the duration of action of sensory block and reduce the required dose of local anaesthetic.[4,24–26] In the present investigation, absence of difference in duration of the sensory block could be related to the low dose of sufentanil. The VAS remained lower throughout the surgical procedure in those patients in whom sufentanil has been added to the local anaesthetic.

Caesarean birth is known to affect breastfeeding in different ways: the initiation of breastfeeding is reduced, the incidence of exclusive breastfeeding is reduced, the onset of lactation is significantly delayed and the likelihood of formula supplementation is increased. Limited evidence is present with respect to increased breastfeeding initiation and decreased time to the first breastfeed with immediate or early skin-to-skin contact after a Caesarean section with subsequent improved maternal satisfaction and bonding and maintenance of the newborn temperature.[7] A more rapid reversal of motor

blockade could reduce the length of stay at the PACU, enhancing breastfeeding initiation with shortened mother–newborn separation. Although 2-CP has a favourable pharmacokinetic profile, resulting in a fast onset of action and a more predictable motor block regression, further studies are needed to confirm reduced length of stay in the PACU. Also, improved conditions for early breastfeeding initiation should be evaluated extensively before clear conclusions.

The incidence of hypotension with the need of vasopressors was equal in all groups.[5,27] The supplementation with colloids and phenylephrine could not always prevent hypotension, though the duration of hypotension was always less than 5 min.

The discussion on the potential neurotoxicity of 2-CP continues.[19] Even 30 years after the first occurrence of severe neurological damage after unintended intrathecal injection of high doses of bisulfite-containing solution of 2-CP, the issue of bisulfite and 2-CP neurotoxicity has not been resolved. Both in vitro and in vivo studies have suggested bisulfite, in the presence of a low pH, as the causative agent.[12] However, a clear link to the neurotoxic effects is inconclusive.[13] This is partly responsible to variable doses of 2-CP, bisulfite and the levels of sulfite oxidase.

In 1980s, there are several cases of neurotoxicity following the inadvertent intrathecal injection of large volumes of 2-CP 3% with bisulfite, though these injections were intended for the epidural space. In our study, we administered small doses of a newly marketed formulation of 1% 2-CP without preservative. This is believed to lower the risk of neurotoxicity.

Further investigation should be done to define the optimal dose of 2-CP and adjuvants such as $\alpha 2$ blockers or opioids and the possible beneficial use for urgent CS.

Limitations of this study include: firstly, the study was not double blinded. The assessing anaesthetist also administered the epidural anaesthesia. Due to organisational reasons, a double-blinded or triple-blinded study was not possible. Secondly, time parameter measurements to determine the peak effect and quality of the sensory block T4-T5 was not performed. These parameters could not be feasibly measured during surgery. Thirdly, this study only used one dose of 2-CP. However, when adapting the dose to weight and disease state of the parturient, the effect may be more beneficial. Fourthly, sample size was relatively small and although no neurotoxicity was found in the present subset of patients, the risk of neurotoxicity still needs investigation. Fifthly, the additional post-operative analgesic needs owing to a more rapid regression of a 2-CP block were not assessed. Sixthly, the clinical events during surgery such as uterine internalisation were not reported with respect to VAS scores.

In conclusion, 2-CP can be used for low-risk Caesarean section in healthy parturients. There is no difference in time to motor block resolution compared to bupivacaine when used in the doses tested in this study. Resolution of motor block seems to be more predictable for 2-CP and may have a benefit on the breastfeeding initiation.

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