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Does spinal chloroprocaine pharmacokinetic profile actually translate into a clinical advantage in terms of clinical outcomes when compared to low-dose spinal bupivacaine? A systematic review and meta-analysis

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ABSTRACT

Study objective: Spinal anesthesia is well suited for day-care surgery, however a persisting motor block after surgery can delay discharge. Among the new drugs available, chloroprocaine has been associated with a short onset time, and motor block duration and a quicker discharge. However, it is not clear if those outcomes are clinically significantly superior compared to those associated with the use of low-dose hyperbaric bupivacaine.
Design: Aim of the study was to determine if spinal 2-chloroprocaine was superior to low-dose spinal bupivacaine regarding the following outcomes: onset time, block duration, time to ambulation and time to discharge.
Patients/interventions: We performed a systematic literature search of the last 30 years using PubMed Embase and the Cochrane Controlled Trials Register. We included only blinded, prospective trials comparing chloroprocaine with a low dose of bupivacaine for spinal anesthesia. Low dose bupivacaine was defined as a dose of 10 mg or less. Outcomes of interest were time to motor block regression (primary outcome), time to ambulation and time to discharge (secondary outcomes), as indirect indicators of a complete recovery after spinal anesthesia.
Main results: Compared to a low dose bupivacaine, spinal 2-chloroprocaine was associated with significantly faster motor and sensory block regression (pMD = −57 min–140.3 min; $P = 0.015$ and < 0.001 respectively), a significantly shorter time to ambulation and an earlier discharge (pMD = −84.6 min; $P < 0.001$ and pMD = −88.6 min and < 0.001 respectively). Onset time did not differ between the two drugs (pMD = −1.1 min; $P = 0.118$).
Conclusions: Spinal 2-chloroprocaine has a shorter motor block duration, a significantly quicker time to ambulation and time to discharge compared to low dose hyperbaric bupivacaine and may be advantageous when spinal anesthesia is performed for day case surgery.

1. Introduction

When performed under spinal anesthesia, procedures characterized by a short duration and a high turnover ideally demand the use of local anesthetics, the pharmacokinetics of which profile allows for a quick recovery and a fast discharge [1].

Lidocaine has an attractive pharmacokinetic profile, with a rapid onset and fast recovery of both sensory and motor block (130–170 min) [2]; however, concerns regarding the risk of transient neurological symptoms (TNS) has limited its widespread clinical use [3–5].

Since its introduction in the 1960s, bupivacaine became the most widespread alternative to lidocaine, showing a lower incidence of TNS; however, its duration of action (240–380 min) might be incompatible with an early rehabilitation and a quick discharge [6]. Moreover, it might cause unpredictable levels of anesthesia, which are dose dependent and may lead to complications, such as hemodynamic instability

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[7–9].

The use of smaller doses of bupivacaine was introduced to avoid these issues; however, low-dose spinal bupivacaine has still been associated to prolonged motor blocks and may lead to an inadequate block height for some surgical procedure [7]. On the other side, Ben-David et al. showed that 7.5 mg of 0.5% hyperbaric bupivacaine can provide adequate spinal anesthesia for ambulatory surgery, when compared with both smaller and larger doses of plain bupivacaine [10].

Recently, 2-chloroprocaine has regained popularity due to its favorable pharmacokinetic properties. It was withdrawn from the market in the 1980s due to concerns about neurotoxicity [11–13] reintroduced in 2004 into clinical practice in a new formulation without preservatives. 2-chloroprocaine shows both a very fast onset (5–10 min) and a quick recovery time (70–150 min) [14,15]. In doses ranging between 30 and 60 mg, spinal block profile is similar to that of lidocaine, with a significantly lower incidence of TNS [16,17].

The clinical characteristics of spinal 2-chloroprocaine are similar to lidocaine [16,17]. However, the impact of the time to motor block regression on patient discharge remain unclear in the literature. Mepivacaine, another short-medium duration local anesthetic, is not registered in many countries for intrathecal use, has a high incidence of TNS and has been compared to lidocaine [18] but not with 2-chloroprocaine for spinal anesthesia.

Bupivacaine using hyperbaric formulation and low doses ($\leq$10 mg) is the main clinically used comparator to 2-chloroprocaine in current ambulatory literature due to its wide spread use and low TNS risk. Therefore, we performed a meta-analysis of blinded, randomised studies comparing low-dose ($\leq$10 mg) hyperbaric bupivacaine to 2-chloroprocaine for spinal anesthesia. Our primary outcome was motor block duration and our hypothesis was that due to its pharmacological characteristics, 2-chloroprocaine would show a significantly shorter motor block regression time.

Secondary outcomes were the time to ambulation, to discharge, sensory onset and offset block time and complication rate.

2. Materials and methods

A systematic review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [19] and the Cochrane Handbook for Systematic Reviews of Interventions [20].

All prospective randomised, controlled trials dealing with ambulatory or inpatient spinal anesthesia were identified using a validated methodology, as described by Dickersin and colleagues [21] performing a computerized search of the electronic databases PubMed, EMBASE and the Cochrane Controlled Trials Register for papers published between May 1987 and May 2017. Only studies in the English language were considered. Maximally expanded search terms with Boolean operators (OR, AND) for the terms “chloroprocaine”, “bupivacaine”, “spinal anesthesia”, “spinal anesthesia”, “low dose”, “motor block”, “sensory block”, “discharge”, “ambulation”, “offset time” and “onset time” were used. Results were further limited by combining with “time to motor block offset” OR “time to motor block remission” OR “time to motor block regression” OR “time to ambulation”, using the Boolean operator AND.

Moreover, the clinical trials database, ClincalTrials.gov, was searched. An additional manual search for theme-related review articles and other relevant material was performed to identify other studies with a ‘snowballing’ technique. The references from all studies were screened for additional literature. Duplicates were eliminated.

We included only double-blind, randomised, controlled trials on adults after written informed consent and ethical committee approval, comparing chloroprocaine with a small dose of bupivacaine for spinal anesthesia. We considered as ‘low dose’ bupivacaine a dose of 10 mg or less, as doses between 5 and 10 mg are considered to be low-dose for lower extremity and abdominal surgery [22].

Outcomes of interest were time to motor block regression (primary outcome), time to ambulation and time to discharge (secondary outcomes), as indirect indicators of a complete recovery after spinal anesthesia. Onset time (secondary outcome) was considered an indirect measure of efficacy. Transient neurologic symptoms (TNS) and postoperative urinary retention (POUR) requiring bladder catheterization were assessed as complications. No restrictions were applied to the technique adopted and the materials used.

Two reviewers independently assessed each title for inclusion (A.S., J.A.), and relevant abstracts were independently evaluated. If doubt existed regarding relevance, the full text article was assessed.

The methodologic quality of all included studies was scored independently by 2 of the authors (A.S. and J.A.) according to a scoring system based on the system developed by Jadad et al. [23] and the modification described in two recent reviews [24,25]. Each study could receive a maximum score of 13. The method of randomization and blinding techniques were considered the most important and could draw a maximum score of 3 points each. All other items could draw a score of 1 point. Studies with scores of 5 or less were considered poor quality and were excluded from further analysis. Those with scores of 6 to 10 were found moderate quality studies and those with scores of 11 or higher were considered good quality studies. Any conflicts in the scoring system were resolved by a third independent reviewer (A.P.).

Data from each of the included studies were successively extracted into an electronic database according to the following parameters: time to motor block regression, time to sensory block regression, time to ambulation, time to discharge.

When data were expressed as medians and interquartile ranges, the first Author of the correspondent study was contacted and asked to provide original rough data in order to calculate means and standard deviations (SD).

As effect estimate, we computed for each study the difference (MD) between the mean times of motor block regression, sensory block regression, onset time, time to ambulation and time to discharge recorded in patients treated with 2-chloroprocaine and bupivacaine, respectively.

To estimate the overall measure of the effect, i.e. the pooled MD (pMD), we computed the weighted mean of the MDs using as weight the inverse of the MD variance, which was estimated as the sum of the deviances of the mean times of each drug divided by the degrees of freedom.

The pooled estimate of the MD was computed using the random effects model following the method of DerSimonian and Laird [26]. This model allowed to estimate the amount of the variability between studies and accordingly provided suitable estimates of the standard errors of the parameters.

The Higgins' I^2 index [26] was calculated to assess the percentage of total cross-study variation due to heterogeneity rather than chance. A forest plot was generated to display results.

We carried out the sensitivity analysis by iteratively recalculating the pooled MD estimate after exclusion of each study at a time. This analysis inspects whether the pooled estimate is strongly dependent on one of the studies collected i.e. if the selection criteria influenced the result of the meta-analysis. The occurrence of publication bias was assessed by visual inspection of the funnel plot and by performing the Egger test to check for *small study effect*.

STATA software was used for all statistical analyses and the generation of forest plot (StataCorp. (2015) Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3. Results

A total of 33 articles were identified using previously described search terms combinations. After analyzing all the articles full text, only four trials matched all the inclusion criteria. From relevant citations and references analysis, no additional studies were identified. Fig. 1

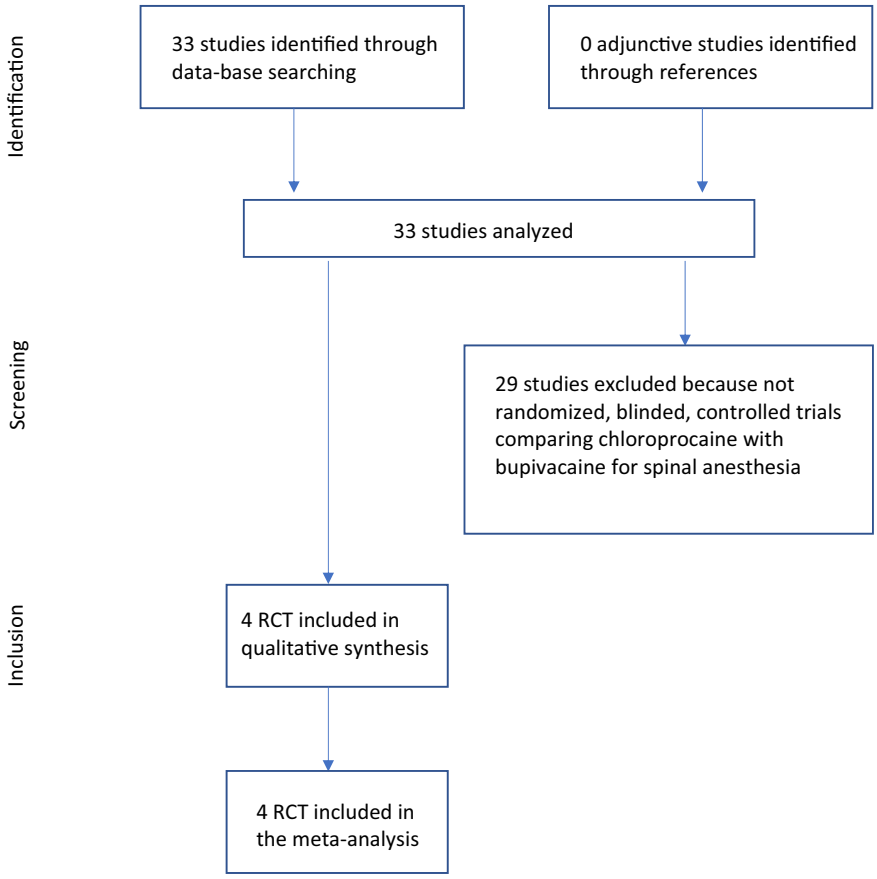

Fig. 1. PRISMA flowchart illustrating the studies selection process.

illustrates the selection process through a PRISMA flowchart.

The four studies included are reported in Tables 1 & 2 [27–30]. These four studies together feature a total of 109 patients treated with 40 mg of 2% 2-chloroprocaine and 114 patients treated with hyperbaric bupivacaine 0.5%. Thus data from a total of 223 patients were pooled and analyzed in this meta-analysis.

All the four studies included were considered of good quality according to the modified Jadad criteria with scores > 11.

Primary outcome (motor block regression time) was present in all the studies included. A subgroup analysis was performed with regard to secondary outcomes on the studies where relative data were present. Time to discharge, sensory block regression and ambulation time were reported in all but one studies, while onset time featuring in only two studies. (Fig. 2).

All outcomes analyzed except onset time, significantly favored 2-chloroprocaine (Fig. 2): when performed with 2-chloroprocaine, spinal anesthesia had similar onset time as if performed with bupivacaine, but was associated with a significantly quicker motor and sensory block regression, which translated into shorter time to ambulation and to discharge.

One study described one case of TNS in each group (7.5 mg hyperbaric bupivacaine 0.75% and 40 mg 2-Chloroprocaine 2%) and no study reported the need of bladder catheterization due to POUR [28]. Excluding time to discharge, heterogeneity is quite large in all endpoints. However, despite that the differences in the times of the two drugs are quite variable, a reduction in favor of 2-chloroprocaine is observed in all studies, making the results of the meta-analysis reliable. In addition, the random effect model, when heterogeneity is high, estimates more accurate confidence intervals of pooled MD than fixed effect model.

Sensitivity analysis reveals that in all endpoints but onset time the difference between mean times remains significant in favor of 2-

Table 1
Studies included in the meta-analysis. Means and standard deviations (SD) are reported for all the assessed outcomes (Bupi: bupivacaine 5%, 2-CP: 2-Chloroprocaine).

	Patients		Motor Block Regression		Onset time		Sensor block regression		Time to ambulation		Time to discharge	
	2-CP	Bupi	2-CP	Bupi	2-CP	Bupi	2-CP	Bupi	2-CP	Bupi	2-CP	Bupi
			mean (sd)	*mean (sd)*	*mean (sd)*	*mean (sd)*	*mean (sd)*	*mean (sd)*	*mean (sd)*	*mean (sd)*	*mean (sd)*	*mean (sd)*
Yoos et al. [30]	8	8	59 (16)	80 (48)	10 (0)	12 (5)	113 (14)	191 (30)	113 (14)	191 (30)	113 (14)	191 (32)
Lacasse et al. [28]	53	53	76 (25)	119 (93)	6 (4)	6 (3)	146 (38)	329 (82)	225 (56)	265 (65)	277 (87)	353 (99)
Maes et al. [27]	18	19	77 (20)	89 (28)	–	–	–	–	–	–	–	–
Teunkens et al. [29]	30	34	90 (25)	180 (78)	–	–	144 (33.6)	306 (76.8)	204 (46.2)	282 (77.4)	276 (79.2)	342 (82.2)

Table 2
Details of studies included in the meta-analysis.

Studies	Sample size 2-CP vs. B	Setting	Sample size justification	Primary outcome	Jadad score
Yoos et al. [30]	8 vs. 8	Randomised, double blind, crossover, volunteer study.	Using a difference of 15 min in time to complete sensory resolution and a standard deviation of 10 min, 8 patients per group were calculated.	Complete sensory resolution	11
Lacasse et al. [28]	53 vs. 53	Randomised, double blind study.	To obtain a 60-min reduction in the eligibility for discharge a minimum of 53 patients per group was required.	Time until discharge	12
Maes et al. [27]	18 vs. 19	Randomised, single blind, controlled study	A sample size of 18 patients per group was required to detect a 15 min difference in regression of motor blockade.	Complete regression of motor blockade	11
Teunkens et al. [29]		Prospective, double blind, randomised controlled study	Sample size to detect a difference in complete recovery of sensory block between the groups and was based on ambulation time that were obtained from the literature for the different local anesthetics. Using a conversion formula, a lognormal distribution for the time until block recovery was assumed for each group.	Time to complete recovery of sensory block	13

2-CP: 2-chloroprocaine, B: bupivacaine.

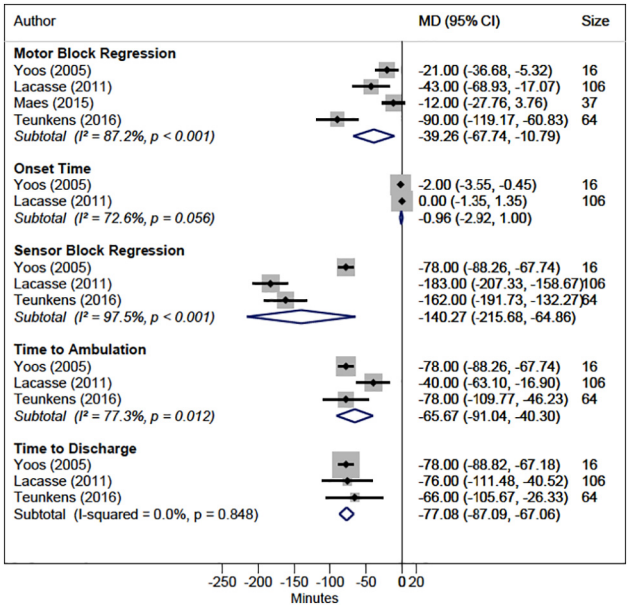

Fig. 2. Forest plot of the studies included in the meta-analysis; data are expressed in minutes; studies left of the line are significantly in favor of lower times related to chloroprocaine use (MD: mean times difference; pMD: pooled mean times difference; CI: confidence intervals).

chloroprocaine.

The funnel plot applied to motor block regression time (Fig. 3), the primary outcome of the studies, shows that the studies were randomly spread around the pooled estimate; moreover, the Eggert test did not suggest the occurrence of the *small study effect* ($P = 0.08$).

4. Discussion

Compared to low-dose bupivacaine, the application of 2-chloroprocaine for spinal anesthesia significantly reduces both motor and sensory block regression time, leading to a significant time reduction to ambulation and consequently time to discharge. Spinal anesthesia onset-time does not differ significantly between the two drugs. Incidence of TNS is similar [28] and no report of postoperative urinary retention (POUR) requiring bladder catheterization was reported in either groups.

These results seem to favor the use of 2-chloroprocaine for spinal anesthesia in ambulatory setting, as this requires reliable blocks, with a quick onset time and a short persistent motor block, leading to a quick recovery and thus a predictable discharge times [31].

Spinal anesthesia performed under the above characteristics is a technique competing with general anesthesia for ambulatory surgery, as shown by a meta-analysis [32]. Liu et al. could show that regional anesthesia leads to decreased post anesthesia care unit use, nausea, and postoperative pain. However, neither central neuraxial block nor peripheral nerve block were associated with reduced ambulatory surgery unit time. Moreover, spinal 2-chloroprocaine has been shown to be favorable for many ambulatory procedures, compared with other short-acting local anesthetics like lidocaine and articaine [33–36]. In these studies, 2-chloroprocaine showed significantly shorter recovery times leading to shorter discharge times. However, despite low-dose bupivacaine has been used in the outpatient setting leading to a reasonably short PACU discharge time of 65–98 min, the risk of primary block failure of 4% seemed excessively high [37]. Furthermore, unilateral spinal anesthesia with 5–7.5 mg of bupivacaine was shown to be inconstant in providing reliable sensory and motor blocks for gynecologic and abdominal surgery [6]. As in some of the included studies, other authors have reported a wide variation in the recovery profiles when bupivacaine was used for spinal anesthesia (with resulting motor block sometimes exceeding 300 min), making bupivacaine not really suitable for outpatient anesthesia [6].

The dose of 2-chloroprocaine in the included studies varied from 40 to 50 mg. Previous dose-finding studies showed that 30 mg was associated with an insufficient duration of analgesia for surgery procedures over 60 min or more, whereas time to complete block resolution was significantly prolonged when a dose of 50 mg is used. A dose of 40 mg thus seems to be a good compromise [38–40]. These results led to the following recommendations by Goldblum and Atchabahian: 30 mg of plain 2-chloroprocaine for surgery up to 40–60 min, 40–45 mg for 45–70 min, and 60 mg for 60–90 min duration respectively [14]. In fact, a dose of 40 mg of 2-chloroprocaine was shown to provide a reliable anesthetic block duration of 60 min, with a time to readiness for discharge of 120 min, with a very low variability [16]. These data are in accordance with the results of our meta-analysis (see Table 1).

Spinal anesthesia interferes with the micturition reflex and bladder function is impaired until the block regresses below the third sacral segment [41]. Thus, bupivacaine or high-dose lidocaine may lead to urinary retention. Risk factors, including male sex, age, history of previous urologic dysfunction, pelvic and prolonged surgery, further increase the risk of POUR [42]. Choi et al. and Mulroy et al. independently suggested in two reviews concrete strategies on how to manage urinary retention [43,44]. Unilateral low-dose spinal anesthesia (6 mg bupivacaine) did not decrease the incidence of urinary retention in high-risk patients [45]. Patients with a low POUR risk apparently have a low incidence of urinary retention after spinal anesthesia with a short-acting local anesthetic compared to general anesthesia [33,46,47]. However, the use of a short-acting local anesthetic does not exclude micturition. Breebaart et al. compared spinal lidocaine to spinal 2-chloroprocaine for outpatient surgery [35]. The two groups

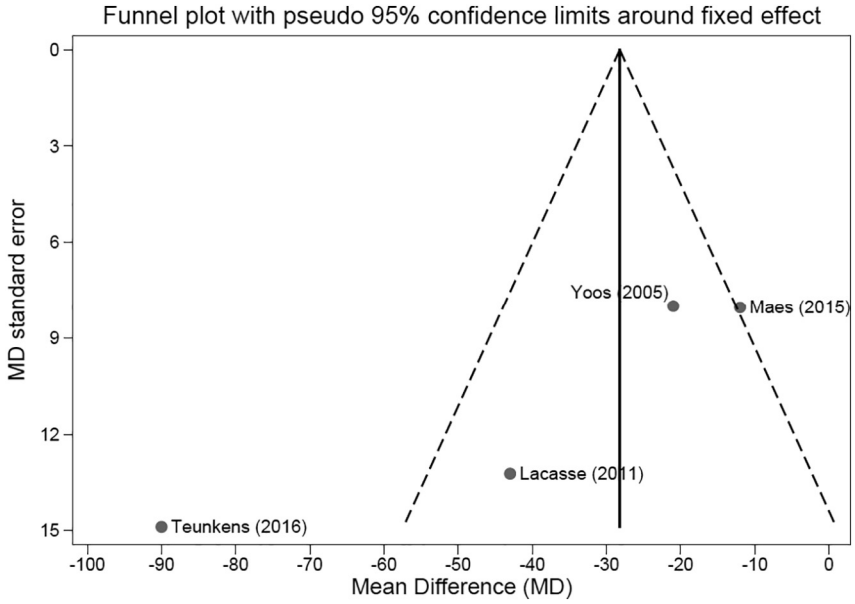

Fig. 3. Funnel plot applied to motor block regression time outcome shows that the studies were randomly spread around the pooled estimate.

received either or not an intravenous preload of 500 mL crystalloid. The preload increased the bladder volume at PACU admission but did not hasten the time to first micturition or discharge. These were not influenced by the type of local anesthetic. However, more micturition problems were encountered in the lidocaine groups, with five bladder catheterizations due to a sensory block above S2 with a bladder volume of > 500 ml. No one case of catheterization in the 2-chloroprocaine groups was reported. This issue is of a practical importance in the outpatient setting, as in many centers spontaneous voiding is a mandatory discharge criterion [44,48,49]. There are no reports of POUR associated to spinal 2-chloroprocaine, which is in accordance with our findings and represents a further potential advantage of this drug in the ambulatory setting [33,35].

In conclusion, spinal 2-chloroprocaine offers a shorter motor block duration leading to a significantly quicker time to ambulation and time to discharge compared to low dose bupivacaine. According to the few available data, 2-chloroprocaine can be recommended when spinal anesthesia is performed for short cases performed in an ambulatory or fast-track setting. However, the impact of these results is limited by the small number of included studies, and further studies will be needed to confirm them.

Declaration of interest

None.

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AB and MC made substantial contributions to the conception and design of the work, the analysis, and interpretation of data for the work and drafting the work for important intellectual content and final approval of the version to be published and is in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JA made substantial contributions to the conception and design of the work, the acquisition, analysis (JA together with AS assessment of literature and its quality), and interpretation of data for the work and revising the work critically for important intellectual content and final approval of the version to be published and is in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AP and DLR made substantial contributions to the conception and design of the work, the statistical analysis of data and their interpretation for the present work. They revised work critically for important intellectual content and gave final approval of the version to be published and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AS, MvdV and AT made substantial contributions to the conception and design of the work and revising the work critically for important intellectual content and final approval of the version to be published and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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