Journal of Clinical Anesthesia 52 (2019) 99–104

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

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

Andrea Saporito[a], Marcello Ceppi[b], Andreas Perren[c], Davide La Regina[d], Stefano Cafarotti[d], Alain Borgeat[e,*], José Aguirre[e], Marc Van De Velde[f], An Teunkens[f]

[a] Anesthesia Department, Bellinzona Regional Hospital, (Switzerland)
[b] Clinical Epidemiology Unit, S. Martino University Hospital, Genoa, (Italy)
[c] Intensive Care Unit, Bellinzona Regional Hospital, Switzerland
[d] Surgery Department, Bellinzona Regional Hospital, Switzerland
[e] Department of Anesthesiology, Balgrist University Hospital, Zurich, (Switzerland)
[f] Department of Anesthesiology, University Hospital of the KU, Leuven, Belgium

ARTICLE INFO

Keywords:
Spinal anesthesia
Chloroprocaine
Ambulatory surgery
Fast-track surgery

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

* Corresponding author at: Department of Anesthesiology, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland.
E-mail address: alain.borgeat@balgrist.ch (A. Borgeat).

https://doi.org/10.1016/j.jclinane.2018.09.003
Received 27 June 2018; Received in revised form 15 August 2018; Accepted 8 September 2018

[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