International Journal of Obstetric Anesthesia (2015) **24**, 237–246
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2015.05.002

ORIGINAL ARTICLE

ELSEVIER
www.obstetanesthesia.com

A systematic review of the effects of adding neostigmine to local anesthetics for neuraxial administration in obstetric anesthesia and analgesia

A.P. Cossu,[a] L.M. De Giudici,[b] D. Piras,[b] P. Mura,[b] M. Scanu,[c] M. Cossu[c], M. Saba[b], G. Finco,[b] L. Brazzi[a]

[a]*UOC Anesthesia and Intensive Care, AOU Sassari, Department of Surgical and Medical Sciences, University of Sassari, Italy*
[b]*UOC Anesthesia and Intensive Care and, Pain Therapy Service, AOU Cagliari, Department of Medical Sciences ''M. Aresu'', University of Cagliari, Italy*
[c]*University of Sassari, Italy*

ABSTRACT

Background: Drugs used in obstetric patients must accomplish two goals: efficacy and safety for both mother and fetus. Neostigmine has been co-administered epidurally and intrathecally with local anesthetics and other adjuncts in the obstetric setting. The aim of this meta-analysis was to assess the efficacy and incidence of adverse events related to the use of neostigmine in obstetric anesthesia.

Methods: A meta-analysis of randomized-controlled human trials was conducted using the data sources Google Scholar and PubMed (updated 1 November 2014). Inclusion criteria were: random allocation to treatment; comparison of neostigmine or neostigmine with local anesthetics and/or other adjuvants versus placebo or placebo with local anesthetics and/or other adjuvants; and approval by an ethics committee.

Results: The use of neostigmine as an adjuvant in neuraxial anesthesia is associated with a reduction in the dose of local anesthetic during labor analgesia and postoperative analgesia following cesarean section: mean reduction of local anesthetic (ropivacaine or bupivacaine) vs. control −4.08 (95% CI −6.7 to −1.5) mg/h (P=0.002). The risk of nausea was increased vs. control with intrathecal neostigmine (OR 8.99 [95% CI 4.74 to 17.05], P <0.001) but not with epidural neostigmine (OR 0.97 [95% CI 0.46 to 2.05], P=0.94). Use of neuraxial neostigmine was associated with a decrease in the risk of pruritus but there was no increase in the incidence of hypotension, dizziness or sedation and no effect on the incidence of abnormal fetal heart rate patterns or Apgar scores.

Conclusions: Neuraxial administration of neostigmine significantly reduces local anesthetic consumption without serious adverse side effects to the mother or fetus. However, neostigmine is only recommended for epidural administration as intrathecal use significantly increases the incidence of maternal nausea and vomiting.

Keywords: Neostigmine; Neuraxial anesthesia; Cesarean section; Labor analgesia

Introduction

Neuraxial anesthesia is considered the gold standard technique in the healthy parturient, providing a good balance of analgesic efficacy and safety for both mother and fetus.[1–3] While local anesthetics administered alone are able to achieve adequate analgesia and anesthesia, the need to extend and enhance their effects without compromising maternal hemodynamics or fetal wellbeing has led to the use of adjuvants. Opioids such as morphine, fentanyl and sufentanil are the main adjuvants in current use.[4–6] Neostigmine, an acetylcholinesterase inhibitor, has been used for both epidural and intrathecal anesthesia in obstetric patients.[7–9] The aim of this meta-analysis was to quantify the benefits and adverse effects of the use of neostigmine as an adjuvant for labor analgesia and postoperative analgesia following cesarean delivery.

Accepted May 2015
Correspondence to: A.P. Cossu, UOC Anesthesia and Intensive Care, AOU Sassari, Department of Surgical and Medical Sciences, University of Sassari, Italy.
E-mail address: andreapcossu@yahoo.it

Methods

We attempted to identify all published studies of the neuraxial use of neostigmine in the obstetric setting where neostigmine was administered in combination with local anesthetics and other adjuvants such as fentanyl or clonidine, using Google Scholar and PubMed (updated 1 November 2014). The full PubMed search strategy included the key words "neostigmine", "intrathecal", "spinal", "epidural", "subarachnoid", "extradural" and "neuraxial technique", "labor analgesia" and "cesarean section" and was developed according to Zangrillo et al.[10] (Appendix A). Our search strategy also included examination of the reference lists of selected articles. References obtained from database and literature searches were first examined independently at the title/abstract level by two investigators, with divergences resolved by consensus.

Inclusion criteria were: random allocation to treatment; comparison of neostigmine or neostigmine with local anesthetics and/or other adjuvants versus placebo or placebo with local anesthetics and/or other adjuvants; and approval by an ethics committee. Exclusion criteria were: duplicate publications; non-human experimental studies; and studies not published in indexed journals. There were no language or publication restrictions. Two investigators selected studies for the final analysis by independently assessing compliance to the selection criteria. Divergences from the selection criteria were resolved by consensus.

Two investigators independently extracted data on study design (including patient selection and treatment allocation), clinical setting, dosages of neostigmine, local anesthetics and other adjuvants in the epidural or subarachnoid space, and experimental duration, with divergences resolved by consensus. If the required data could not be extracted from the published report, at least two separate attempts at contacting the original authors were made before exclusion. Abstracts from international congresses published in indexed journals were also included. The primary end-point was the evaluation of the efficacy of neuraxial neostigmine and its effect on local anesthetic dose when used for cesarean section or labor analgesia. The co-primary end-point was the incidence of adverse effects during labor or during the postoperative period following cesarean section.

Statistical analysis

Binary outcomes and continuous variables from individual studies were analyzed according to the Mantel-Haenszel model to compute individual odds ratios (OR) with 95% confidence intervals (CI), and a pooled summary effect estimate was calculated by means of the fixed-effect model. Statistical heterogeneity and inconsistency were measured using Cochran Q tests and I^2 (by Higgins and Thompson), respectively.[11] The risk of publication bias was assessed by visual inspection of funnel plots. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing and at 0.10 for heterogeneity testing. According to Higgins et al. I^2 values around 25%, 50%, and 75% were considered to represent low, moderate and severe statistical inconsistency respectively.[11] Computations were performed with RevMan 4.2 (freeware available from the Cochrane Collaboration).[12]

Results

Database searches and contacts with experts yielded a total of 57 citations. After excluding non-pertinent titles or abstracts, 15 studies were retrieved in complete form and assessed according to the selection criteria (Fig. 1). Three studies were excluded for the following reasons: one study did not have a randomized design,[9] one was not performed in an obstetric surgical environment[13] and one did not have a comparator to neostigmine.[14] Twelve eligible clinical trials[15–26] and four abstracts[27–30] were identified and included in the final analysis (Table 1).

The 16 studies included 1183 patients; 666 patients received neostigmine with local anesthetic and opioid with or without clonidine or other adjuvants; 517 patients received local anesthetic and opioid with placebo or other adjuvants but not neostigmine. Neostigmine was administered epidurally to 536 patients and 372 controls. In addition, 130 patients who received neostigmine intrathecally were compared with 145 controls. The dose of neostigmine varied across studies. Doses of neostigmine, local anesthetics, opioids and clonidine are shown in Table 2.

Overall analysis showed that, in comparison with the controls, neostigmine was associated with a reduction in the dose of local anesthetic during labor analgesia and for postoperative analgesia following cesarean section (mean reduction of local anesthetic [ropivacaine or bupivacaine] −4.08 mg/h [95% CI −6.7 to −1.5], P=0.002 for effect, P <0.01 for heterogeneity, I^2=92%, Fig. 2). There were no differences in labor duration and time to first rescue dose. Neostigmine was only administered epidurally in the eight studies of labor analgesia included in the analysis.

Neostigmine was associated with an increased risk of nausea after neuraxial administration (neostigmine 103/419 vs. control 35/292, OR 3.12 [95% CI 1.18 to 8.21], P=0.02 for effect, P <0.01 for heterogeneity, I^2=67%, Fig. 3A). The risk of nausea was increased with intrathecal administration (neostigmine 72/110 vs. control 22/125, OR 8.99 [95% CI 4.74 to 17.05], P <0.001 for effect, P=0.22 for heterogeneity, I^2=32%, Fig. 3B) but not with epidural administration (neostigmine 31/309 vs. control 13/167, OR 0.97 [95% CI 0.46 to 2.05], P=0.94 for effect, P=0.85 for heterogeneity, I^2=0%, Fig 3C). The risk of nausea was increased in