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Review Article

REVIEW ARTICLE

The impact of neuraxial clonidine on postoperative analgesia and perioperative adverse effects in women having elective caesarean section—a systematic review and meta-analysis

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Abstract

Neuraxial clonidine improves postoperative analgesia in the general surgical population. The efficacy and safety of neuraxial clonidine as a postoperative analgesic adjunct in the caesarean section population still remains unclear. This systematic review and meta-analysis aims to evaluate the effect of perioperative neuraxial clonidine on postoperative analgesia in women having caesarean section under neuraxial anaesthesia. We included randomized controlled trials comparing the analgesic efficacy of the perioperative administration of neuraxial clonidine alone or in combination with a local anaesthetic and/or opioids in women having elective caesarean section under neuraxial anaesthesia when compared with placebo. PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE were searched until February 2017. Eighteen studies were included in the meta-analysis. Neuraxial clonidine reduced 24 h morphine consumption [mean difference (MD): −7.2 mg; 95% confidence interval (CI): −11.4, −3.0 mg; seven studies] and prolonged time to first analgesic request (MD: 135 min; 95% CI: 102, 168 min; 16 studies) when compared with the control group. Neuraxial clonidine increased intraoperative hypotension [odds ratio (OR): 2.849; 95% CI: 1.363, 5.957], intraoperative sedation (OR: 2.355; 95% CI: 1.016, 5.459), but reduced the need for intraoperative analgesic supplementation (OR: 0.224; 95% CI: 0.076, 0.663). The effect of clonidine on intraoperative bradycardia, intraoperative and postoperative nausea and vomiting, postoperative sedation, and pruritus were inconclusive. Neuraxial clonidine did not negatively impact neonatal umbilical artery pH or Apgar scores. This review demonstrates that neuraxial clonidine enhances postoperative analgesia in women having caesarean section with neuraxial anaesthesia, but this has to be balanced against increased maternal adverse effects.

Keywords: adrenergic alpha-2 receptor agonist; caesarean section; clonidine

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Caesarean section is one of the most common surgical procedures performed in the obstetric patient population.[1] Pregnant women rate pain during and after caesarean delivery as their primary concern.[2] The postoperative management of pain after caesarean section still remains a challenge. Poorly controlled acute postoperative pain can affect a new mother's mobility, mood, and ultimately her ability to care for her newborn baby.[3] Poorly controlled acute postoperative pain also increases the risk for persistent pain for up to 8 weeks postpartum.[3] Current strategies for the management of postoperative pain mainly involve the use of neuraxial opioids when neuraxial anaesthetic techniques are used. Even though neuraxial opioids have improved the quality of postoperative analgesia, they are associated with opioid related side effects such as nausea, vomiting, and pruritus.[4] Additionally, in an increasing number of opioid tolerant patients, opioids may be less effective.[5] Furthermore, in some countries long-acting opioids such as preservative-free morphine or diamorphine may not be readily available. As a result, there is renewed interest in the use of non-opioid analgesic adjuncts administered via the neuraxial route, such as clonidine, for the optimization of postoperative pain after caesarean section.

Clonidine is an α_2 agonist that mediates its analgesic effect via the α_2 receptor located post-synaptically on the dorsal horn of the spinal cord. Stimulation of the α_2 receptor reduces afferent transmission of pain producing analgesia.[6] In the general surgical population, the administration of i.v. clonidine to patients receiving general anaesthesia reduced morphine consumption and pain scores at 24 h after surgery, when compared with placebo.[7] Similarly, the administration of clonidine intrathecally enhanced the effect of local anaesthetics and opioids resulting in a longer time to first request for analgesia and a reduction in 24 h morphine consumption.[8,9] The analgesic effect of neuraxial clonidine for post-caesarean analgesia still remains unclear, with studies investigating its analgesic effect yielding conflicting results. Recent evidence also suggests that clonidine may reduce acute hyperalgesia and possibly the development of chronic persistent pain after caesarean section.[10] However, while clonidine may improve post-caesarean delivery analgesia, it has been associated with an increased incidence of maternal hypotension, sedation, and foetal acidosis, limiting its clinical use.[8,11]

To address these concerns we performed a systematic review and meta-analysis to evaluate the effect of perioperative neuraxial clonidine administration on postoperative analgesia in women having caesarean section under neuraxial anaesthesia. Our hypothesis was that in women having caesarean section under neuraxial anaesthesia, the administration of neuraxial clonidine would improve postoperative analgesia. This improvement would be determined by a reduction in morphine consumption and/or an increase in the time to first analgesic request, our primary outcomes of interest. We also investigated whether the administration of clonidine would be associated with a reduction in maternal opioid related side effects. Finally, we investigated whether the administration of clonidine would be associated with an increase in maternal or foetal adverse effects.

Methods

This systematic review and meta-analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[12]

Eligibility criteria

We performed a search of the published literature for randomized controlled trials comparing the analgesic efficacy of the perioperative administration of single or multiple doses of neuraxial clonidine alone or in combination with a local anaesthetic and/or opioid in women having elective caesarean section under neuraxial anaesthesia when compared with placebo. Specifically, these trials needed to report 24 h opioid analgesic consumption (or the closest time point) and/or time to first analgesic request in both experimental arms. When studies reported multiple treatment arms using additional non-narcotic adjuncts, only data from the groups utilizing an amide local anaesthetic (with/without opioid) and clonidine (with/without opioid) were extracted. We included studies where neuraxial clonidine was administered in addition to short and long acting neuraxial opioids for surgical anaesthesia and/or postoperative analgesia. However, we excluded studies where clonidine was co-administered with differing doses of opioids for determining synergism or relative potency. We also excluded studies where the dose of local anaesthetic was different in the control and treatment arms of the study and where neuraxial clonidine was administered in patients who received general anaesthesia. Data from abstracts and unpublished trials were excluded. Eligibility was assessed independently by two individuals (T.K.A. and B.M.M.). Disagreements were reconciled by discussion and then by a 3rd member of the study team (A.S.H.) when necessary.

Search strategy

We searched PubMed (1966–2017), the Cochrane Central Register of Controlled Trials, and EMBASE using the search strategies described in the supplementary file up to February 2017. We imposed no language restrictions. The bibliographies of retrieved trials were also used to identify other relevant articles. Where appropriate, authors were contacted for missing or additional data. The methodological quality of included studies was assessed by two persons (T.K.A. and R.Y.K.) using the Cochrane collaboration tool for assessing risk of bias. Included studies were assessed for selection bias, performance bias, detection bias, attrition bias, and reporting bias.[13] Studies were assessed as low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for any of the key domains), or high risk of bias (high risk of bias for one or more key domains).[13]

Data were extracted and entered in a Microsoft Excel® (Microsoft Corporation, WA, USA) spreadsheet independently by two authors (T.K.A. and B.M.M.) and checked for accuracy by a 3rd author (R.Y.K.). We extracted data on the country where the study was performed, neuraxial anaesthetic technique, type and dose of local anaesthetic administered, type and dose of neuraxial opioid administered, timing of administration and route of administration (spinal *vs* epidural) of neuraxial clonidine, and postoperative analgesic regime. We also extracted data on:

1. Our primary outcomes: i.v. morphine consumption at 24 h (or closest reported time point) and the time to first analgesic request. When studies reported postoperative analgesic consumption using other opioids or anti-inflammatory agents, they were converted to i.v. morphine equivalents using the following conversion factors: i.v. ketorolac 30 mg was equivalent to 10 mg of i.v.