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What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials

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ABSTRACT

Study objective: A place for clonidine has been suggested for many indications in perioperative medicine. The aim of this systematic review and these meta-analyses is to systematically, and quantitatively, evaluate these potential indications of clonidine.
Design, setting, patients and interventions: We selected and analyzed (qualitatively and, when possible, quantitatively) the available literature published on PubMed/Medline and on the Cochrane database. Inclusion criteria included: human randomized controlled trials involving adults who received perioperative systemic (oral, intramuscular, transdermal and intravenous) clonidine for every type of surgery.
Measurements and main results: We identified 775 trials and thereafter excluded 718 and analyzed 57 trials concerning, in total, 14,790 patients of whom 7408 received clonidine and 6836 received placebo. Most important results shows that, in qualitative and quantitative analyses, clonidine vs placebo reduces analgesics consumption in, respectively, (159 vs 154 patients: 24%, 95%CI[16%–32%]; $p < 0.001$), reduces nausea and vomiting (risk ratio, in 180 vs 181 patients: 0.35, 95%CI[0.25–0.51]; $p < 0.001$), improves hemodynamic stability (reduction of HR: 14.9 bpm, 95%CI[10.4–19.5]; $p < 0.001$; reduction of the MAP: 12.5 mm Hg, 95%CI[7.14–17.86]; $p < 0.001$); 1 min after tracheal intubation, in 67 vs 68 patients), prevents postoperative shivering (risk ratio, in 140 vs 140 patients: 0.17, 95%CI[0.10–0.29]; $p < 0.001$). On the other hand, clonidine does not have any influence on renal and cardiac outcomes (adverse events rates, in 5873 vs 5533 patients: 0.00, 95%CI[−0.10–0.11]; $p = 0.96$) and does not prolong awakening time.
Conclusions: In conclusion, these systematic review and meta-analyses of 57 trials confirm that clonidine improves pain control, reduces PONV, improves hemodynamic and sympathetic stability, with no adverse consequences on renal function or awakening time, but does not influence cardiac outcome in the general population, after non-cardiac surgery. Nevertheless, given the high heterogeneity between the studies, this does not exclude different results in patient subgroups or specific procedures.

Contents

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1. Introduction

After the results of the PeriOperative Ischemic Evaluation-2 (POISE-2) study, a large multicentric study, suggesting that clonidine does not improve the cardiac outcome of the patients in non-cardiac surgery [1], it appears important to evaluate if clonidine has still a place in anesthesia. Indeed, these negative results may introduce doubts concerning the added value of clonidine in the perioperative period. A definitive evidence in other indications than prevention of myocardial infarction may help the anesthesiologist to have a clear vision about the place of clonidine.

Undergoing anesthesia and surgery is associated with specific risks and complications before, during and after the procedure. To provide patient comfort and safety is the objective of the anesthesiologist.

Clonidine is a centrally acting imidazolin α2-adrenergic agonist, analog of norepinephrine. The pre-synaptic stimulation of α2-receptors is coupled via G-protein to several effectors including inhibition of adenylate cyclase and effects on potassium and calcium channels [2] that finally restricts the release of norepinephrine in the central nervous system (in the nucleus tractus solitaries and nucleus reticularis lateralis region of rostroventro-lateral medulla). Clonidine was synthesized for the first time in 1962 in Germany. At the beginning it was commercialized as antihypertensive drug and many years later his use in anesthesia started for its marked sedation properties. Clonidine is rapidly absorbed after oral administration with a time to maximum plasma concentration between 1.5 and 2 h [3] and has a half-life approximately 8–12 h [4,5]. This implies a possible place to target intra- and postoperative events.

This drug has been largely studied in anesthesia, suggesting a place for analgesia, antiemesis, bleeding reduction, induction time reduction, hemodynamic and hormonal stability, reduction of oxygen consumption, renal protection, anesthetics-sparing effect, anxiolysis, sedation, antishivering, recovery time reduction and myocardial protection.

The aim of these systematic review and meta-analyses is to systematically evaluate these potential indications of clonidine.

2. Methods

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations [6], we selected and analyzed the available literature published on PubMed/Medline and on the Cochrane database.

2.1. Information sources, eligibility criteria and study selection

We screened the PubMed/Medline (1966 – November 2014) and the Cochrane database using the terms “clonidine” AND (“anaesthesia” or “anesthesia”). We used the PICOS framework (patient, intervention, comparison, outcome and study design) as proposed in the PRISMA statement. Inclusion criteria included the facts that the studies were human randomized controlled trials involving adults (aged >18 years) who received systemic (oral, intramuscular, transdermal and intravenous) clonidine pre, per or postoperative undergoing local, regional or general anesthesia for every type of surgery, testing its different effects. As our goal was to evaluate all the potential indications of clonidine, no restriction was done on this field. Studies with no appropriate data reporting (e.g. size effect in term of mean response) were excluded from the quantitative analyses, and, eventually, from the qualitative analyses. Missing data were considered as such. All articles identified through the literature search were reviewed for inclusion by one author (MCSM) with the help of another author (PF). Queries were solved by consensus method between both authors (MCSM and PF).

2.2. Data collection

Firstly, one author (MCSM) screened the references identified by the search strategy by title and abstract. After the selection of the clear and complete references, relevant information from the original papers was extracted. Incomplete or unclear reports were excluded. Finally the second author involved in data collection (PF) independently checked the extracted data. The Cochrane Collaboration's tool was used for assessing risks of bias at the study level (including funnel plots). Only publications in English were included (for full methodology, see the Appendix).

2.3. Data extraction

Extracted information included authors, country, date of publication, study design, type of surgery, type of anesthesia, number of participants, age, ASA score, clonidine dose(s), route of administration and timing.

In addition for every single effect of the clonidine studied we extracted specific and relevant information, as detailed in the Appendix. Finally we also extracted data on adverse events.