Effect of perioperative systemic alpha-2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials

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CRD summary
The review concluded that perioperative systemic alpha-2 agonists decreased opioid consumption, pain intensity, and nausea, after surgery under general anaesthesia, without affecting recovery time. Given the evidence of clinical and statistical variation, and the small trials with quality issues, caution is advised when interpreting the authors’ results and conclusions.

Authors’ objectives
To determine the efficacy of perioperative systemic alpha-2 agonists on postoperative morphine consumption and pain intensity in patients undergoing surgery under general anaesthesia.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2011 for published articles in any language. Search terms were reported and the reference lists of retrieved articles were searched.

Study selection
Randomised controlled trials of systemic alpha-2 agonists administered before, during or after surgery, versus placebo or no treatment were eligible for inclusion if they included at least 10 adults in each group who underwent non-cardiac surgery under a general anaesthetic. Trials had to report data on postoperative cumulative opioid consumption, postoperative pain intensity, or both. For pain intensity, visual analogue scales from zero to 10cm had to be used.

The included trials studied clonidine or dexmedetomidine at various doses, administered by intravenous bolus or continuous infusion. The comparator was generally placebo, but some trials used no treatment. Alpha-2 agonists were only given before surgery in 10 trials, during surgery in six trials, and after surgery in four trials, and given throughout the perioperative period in 10 trials. Where specified, the type of surgery was abdominal; hysterectomy; spine; ear, nose and throat; orthopaedic; or vascular. Trials were conducted between 1990 and 2009 in 16 different countries, including Turkey, China and the USA.

One reviewer undertook study selection, and queries were resolved by discussion with two other reviewers.

Assessment of study quality
Quality was assessed using a modified four-item Oxford scale, which appraised randomisation, allocation concealment, blinding, and follow-up, to give a score out of seven. One reviewer assessed quality and the results were independently checked by a second reviewer; disagreements were resolved through discussion with a third reviewer.

Data extraction
One reviewer extracted data on opioid consumption, pain intensity and adverse events, to calculate mean differences and risk ratios, with 95% confidence intervals. For opioid consumption, all doses of non-morphine opioids were converted to morphine equivalents. A second reviewer checked the extracted data for accuracy. Trial authors were contacted for missing data.

Methods of synthesis
A fixed-effect meta-analysis was undertaken to calculate pooled weighted mean differences and risk ratios, together with 95% confidence intervals. Statistical heterogeneity was assessed using I² and X². Where significant heterogeneity was detected a random-effects model was used. The number needed to treat and the number needed to harm were calculated for statistically significant results. Trials were analysed separately for clonidine and dexmedetomidine.

Results of the review
Thirty trials were included, with 1,792 participants; 19 trials were on clonidine and 11 trials were on dexmedetomidine. Trial sample size ranged from 24 to 200 patients. The quality of the trials ranged from two to seven (median four); only one trial reported allocation concealment.

Compared with control, clonidine was associated with statistically significantly lower postoperative morphine use at 24 hours (WMD -4.1mg, 95% CI -6.0 to -2.2; I²=0; four trials), as was dexmedetomidine (WMD -14.5mg, 95% CI -22.1 to -6.8; I²=91%; six trials).

Compared with control, clonidine was associated with statistically significantly lower pain intensity at 24 hours (WMD -0.7cm, 95% CI -1.2 to -0.1; I²=51%; four trials), as was dexmedetomidine (WMD -0.6, 95% CI -0.9 to -0.2; I²=33%; three trials); but at 48 hours the difference was no longer statistically significant.

Both clonidine and dexmedetomidine were associated with a reduction in early nausea. Clonidine increased the risk of intraoperative (NNH nine) and postoperative (NNH 20) hypotension, whilst dexmedetomidine increased the risk of postoperative bradycardia (NNH three). There was no difference in recovery times.

**Authors' conclusions**
Perioperative systemic alpha-2 agonists decreased opioid consumption, pain intensity and nausea, after surgery, with no difference in recovery time. Common adverse events were bradycardia and hypotension.

**CRD commentary**
The inclusion criteria for the review were appropriately defined and several relevant databases were searched for articles in any language. Publication bias was not assessed and cannot be ruled out. Attempts were made to reduce reviewer error and bias throughout the review. Quality assessment indicated that some of the evidence was not optimal. Data were pooled using meta-analysis; there was evidence of significant statistical heterogeneity in several of the analyses, which was not explored. There was evidence of clinical differences between trials in the surgery and treatments. The authors noted that the small sample sizes could have biased the results.

Given the evidence of clinical and statistical variation, and the small trials with quality issues, caution is advised when interpreting the authors’ results and conclusions.

**Implications of the review for practice and research**
**Practice**: The authors stated that when making clinical decisions, the analgesic benefits of alpha-2 agonists should be balanced against the risks of hypotension and bradycardia, during and after surgery.

**Research**: The authors stated that the best dose and time of administration for alpha-2 agonists required further study and longer trials were needed. The effects of alpha-2 agonists on chronic postoperative pain and hyperalgesia should be determined. For alpha-2 agonists to be used in practice, evidence was needed for the regimens that provide maximum benefit and minimum harm.

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