Efficacy and safety of clonidine as additive for caudal regional anesthesia: a quantitative systematic review of randomized controlled trials
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CRD summary
The review concluded that, compared to caudal local anaesthetics alone, caudally administered clonidine in addition to local anaesthetics provided extended duration of analgesia with a decreased incidence for analgesic rescue requirement and few adverse events. The review was generally well conducted but, due to substantial heterogeneity and potential publication bias, the authors' conclusions should be considered tentative.

Authors' objectives
To assess the efficacy and safety of caudal clonidine in addition to local anaesthetics in comparison with local anaesthetics alone in children undergoing urological, lower abdominal or lower limb surgery.

Searching
MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1981) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant studies; search terms were reported. The reference lists of retrieved studies were also searched for other relevant studies. Research groups working on the topic were contacted for ongoing trials.

Study selection
Prospective randomised controlled trials (RCTs) that assessed caudally administered clonidine in addition to local anaesthetics in comparison with local anaesthetics alone in children undergoing surgery were eligible for the review. Primary outcomes of interest were duration of postoperative analgesia (defined as time from caudal injection until the first requirement of rescue analgesia), number of patients requiring rescue analgesia and total number of postoperative rescue requirements. Secondary outcomes included number of children with adverse events such as: postoperative nausea and vomiting; respiratory depression; sedation; bradycardia; hypotonia; delayed motor function; delayed micturition; and neurological complications.

In the included studies, participants were children aged two to six years. Local anaesthetics included bupivacaine, ropivacaine, levo bupivacaine or mepivacaine. Clonidine was administered in four different doses: 1.0, 1.5, 2.0 and 5.0 ug kg\(^{-1}\). Some trials also included other additives such as ketamine, epinephrine, dexmedetomidine or opioids. Some studies reported an intravenous induction with thiopental or propofol.

Two reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality using the Jadad scale; criteria included random allocation, concealment of allocation, blinding technique and description of withdrawals.

Two reviews independently assessed studies for quality using standardised forms.

Data extraction
Data were extracted and relative risks (RRs) for dichotomous data and mean differences (MDs) for continuous data, with corresponding 95% confidence intervals (CIs), were calculated. Where there were queries about the data, the authors of some of the included studies were contacted for clarification.

Two reviewers independently extracted data on to standardised forms, with disagreements resolved by discussion or by referring to a third reviewer.

Methods of synthesis
Where possible, studies were pooled in meta-analyses then summary effect relative risks and mean differences (with
corresponding 95% confidence intervals) were estimated using a fixed-effects model, if no heterogeneity was identified. Statistical heterogeneity was assessed with χ² and quantified using I² (I² value greater than 30% was considered evidence of heterogeneity). If significant heterogeneity was identified, analyses were undertaken using the random-effects model. Where continuous data reported a median, the data were not used in analyses. Statistical and clinical heterogeneity were further explored in sensitivity and subgroup analyses. Subgroup analyses assessed the effects of different types of local anaesthetics, different doses of long lasting anaesthetics and different doses of clonidine (1 to 2ug kg⁻¹). Sensitivity analysis assessed the effects on results of different methodological quality of the included studies and the use of epinephrine in either the treatment or control group. Publication bias was assessed with a funnel plot.

Some outcomes were synthesised narratively.

Results of the review
Twenty RCTs (993 children) were included in the review. Most studies were considered to have been moderate quality; one study was low quality with a Jadad score below 3. Most studies were double blind (observer and participants) and nine had adequate allocation concealment. All studies provided adequate descriptions of drop-outs.

Compared to local anaesthetics alone, anaesthetics with clonidine were associated with a significantly longer duration of postoperative analgesia (MD 3.98 hours, 95% CI 2.84 to 5.13; significant heterogeneity; I²=88%; 13 trials) and a significantly lower proportion of participants requiring postoperative rescue medications during the 24 hour study period (RR 0.72, 95% CI 0.57 to 0.90; significant heterogeneity; I²=53%; nine trials). Subgroup and sensitivity analyses undertaken for duration of analgesia did not find markedly different results to the overall analysis.

Three of six trials found that the number of post operative rescue medications was significantly lower in the combined clonidine group when compared to the anaesthetics alone group. The incidence of complications was low in both groups and there was no evidence of a statistical difference between groups in any of the assessed complications.

There was some evidence of publication bias.

Authors’ conclusions
There was considerable evidence that, compared to caudal local anaesthetics alone, caudally administered clonidine in addition to local anaesthetics provided extended duration of analgesia, with a decreased incidence of analgesic rescue requirement and few adverse events.

CRD commentary
The review addressed a clear research question, supported by appropriate inclusion criteria. A range of relevant sources were searched for studies without language or publication restriction, which minimised the chance of language or publication bias. Appropriate methods were used to select studies, extract data and assess studies for quality, which minimised the chance of reviewer error and bias.

A valid tool was used for quality assessment and the included studies were generally of moderate quality. Substantial statistical heterogeneity and apparent clinical variation (acknowledged by the authors) meant that the use of a random-effects model to pool studies was likely to have been appropriate. The authors attempted to explain the heterogeneity and suggested that type, concentration and drug doses may have influenced the results. In addition, there were different pain thresholds between studies at which rescue analgesics were administered, which further contributed to the variability. Asymmetry of the funnel plot for duration of analgesia meant that publication bias could not be excluded. The review was generally well conducted but, due to substantial heterogeneity and potential publication bias, the authors' conclusions should be considered tentative.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice but noted that caudally administered clonidine was off-label.

Research: The authors did not state any implications for research.

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