A qualitative systematic review of peri-operative dextromethorphan in post-operative pain

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CRD summary
This well-conducted review assessed the benefits and side-effects of dextromethorphan in treating post-operative pain. The authors stated that dextromethorphan is potentially a useful and safe agent for the management of post-operative pain. However, they were unable to recommend its use in clinical practice or an appropriate treatment regimen. The authors' conclusions are appropriately cautious given the variability of the data included in the review.

Authors' objectives
To evaluate the analgesic efficacy and side-effects of peri-operative dextromethorphan in treating post-operative pain.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from inception to February 2005 using the terms 'dextromethorphan', 'post-operative pain' and 'pain-post-operative' alone and in different combinations. The reference lists of retrieved articles were handsearched for additional studies. Only full reports of published studies were considered.

Study selection
Study designs of evaluations included in the review
Randomised double-blind clinical trials (RCTs) were eligible for inclusion. Studies with less than 10 participants were excluded. The numbers of participants in the included studies ranged from 35 to 120.

Specific interventions included in the review
Studies of parenteral or oral dextromethorphan (DM) compared with placebo were eligible for inclusion. In the included studies, DM was administered either pre- or post-operatively to treat post-operative pain; surgical procedures included haemorrhoidectomy, upper abdominal surgery, radical mastectomy, laparoscopic cholecystectomy and total knee replacement. Parenteral doses ranged from 10 to 120 mg and oral doses (once or twice pre-operatively, or repeated doses pre- and post-operatively) from 13 to 240 mg.

Participants included in the review
Patients undergoing any type of surgery were included. Three of the included studies were conducted in children. The included studies reported the following types of surgery: abdominal surgery, haemorrhoidectomy, mastectomy, cholecystectomy, knee replacement, tonsillectomy, hysterectomy, abortion, bone-malignancy resection and lower body surgery.

Outcomes assessed in the review
The primary outcome measures included mean pain scores at rest (early 0 to 6 hours; late 6 to 24 hours), time to first analgesic request and supplemental opioid consumption in the observation period (time to first consumption and dose). Other outcomes reported in the review include opioid-related side-effects.

How were decisions on the relevance of primary studies made?
All of the authors independently assessed studies for relevance. Consensus was reached by discussion.

Assessment of study quality
The studies were assigned a quality score using the Jadad scale (randomisation, allocation concealment, blinding, and losses to follow-up). Given that only double-blind RCTs trials were included, the minimum score attainable was 2 and the maximum was 5. All of the authors independently assessed the validity of the studies. Consensus was reached by discussion.
Data extraction
One reviewer recorded the data onto standardised collection sheets which were checked by the other reviewers. In addition to the standard types of study data, the administration and assessment times, observation period and type of operative anaesthesia were recorded. Due to difficulties in detecting an improvement with low or no pain, it was noted if pain scores in the study groups were less than 30 mm on the visual analogue scale. Odds ratios, number-needed-to-treat, number-needed-to-harm and weighted mean differences could not be calculated because of the inadequacies of the reported data.

Methods of synthesis
How were the studies combined?
A meta-analysis was intended, but substantial differences in the methodology and reporting of the trials made this inappropriate. A narrative synthesis was used instead.

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review.

Results of the review
Twenty-eight double-blind placebo-controlled RCTs (n=1,629), including 40 comparisons, were included. A total of 906 participants received DM.

The median quality score for the included studies was 4 (range: 2 to 5), with 16 studies scoring 4 or 5 out of a possible 5 points. DM did not produce a clinically significant reduction in the post-operative pain score. However, the time to first analgesic request was significantly prolonged with DM in most comparisons. In addition, significant decreases in supplemental opioid consumption were observed in the majority of parenteral DM studies and in about one-half of the oral studies. These decreases were, however, of questionable clinical importance in most comparisons, but a relationship between a decrease in opioid consumption and opioid-related side-effects was established in some studies. Overall, very few DM-related side-effects were reported in the studies.

Authors' conclusions
Dextromethorphan has the potential to be a safe adjunctive agent to opioid analgesia in post-operative pain management, but the consistency of the potential opioid-sparing and pain-reducing effect must be questioned. The route of administration may be important for the beneficial effect.

CRD commentary
This was a generally well-conducted review, though its findings were limited by the quality of the included studies and their substantial variability. Appropriate methodology was used throughout the review process to reduce the risk of bias, although publication bias may be an issue due to the exclusion of abstracts and unpublished data. Given the variability in the studies, the authors presented a concise synthesis of their findings supported by clearly presented tables of data. However, they noted that nine of the 10 parenteral studies were conducted by the same research group, which may bias the data. The findings of the review appear to be supported by the data presented, and the authors are rightly cautious in their conclusions given the limitations of the studies.

Implications of the review for practice and research
Practice: The authors stated that it was not possible to recommend dose regimens or the routine clinical use of DM in post-operative pain management.

Research: Future studies should investigate the importance of the route of administration of DM and use of standardised outcome measures for the comparison and interpretation of clinical results.
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