Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task

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Authors' objectives

To assess the efficacy of extradural clonidine in the relief of post-operative pain, to determine whether anti-nociceptive effects and side-effects were dose-related, and to what extent the latter were deleterious.

Searching

The databases of MEDLINE and Excerpta Medica were searched from 1985 to 1997 using the following headings: regional analgesia; extradural clonidine; postoperative analgesia; and postoperative pain. Citations from articles were cross-referenced with those in the assessor's bibliography and those of the articles under review.

Study selection

Study designs of evaluations included in the review

Randomised controlled double blind trials (RCTs) that evaluated extradural clonidine in the relief of post-operative pain were included if they had clearly defined objectives and adequate statistical analysis.

Specific interventions included in the review

Extradural clonidine, injected in the following ways, was studied: bolus injection alone, bolus followed by continuous infusion; bolus followed by patient-controlled analgesia infusion; bolus injection of a mixed solution followed by continuous solution; a mixed solution combining clonidine with fentanyl, local anaesthetics, two or more of these drugs, and continuous infusion of clonidine and morphine. Clonidine-bolus doses ranged from 75 to 800 micrograms, and from 1 to 8 micrograms/kg, and continuous infusions ranged from 0.3 to 2.0 micrograms/kg/hour and from 10 to 50 micrograms/hour. Administration was either intra-operatively, a few minutes after induction of anaesthesia, at the beginning of the surgical procedure, 30 minutes before the end of the surgical procedure, or post-operatively on arrival in the recovery room, 1-hour after surgery, or at the patients' first complaint of pain. Extra-dural catheters were inserted either thoracically or at the high and/or the low lumbar level. Additional analgesics were given via patient controlled analgesia, extradurally, intravenously, subcutaneously or intramuscularly and included morphine, pethidine, sufentanil, paracetamol, piritramide, ketoprofen and bupivicaine-fentanyl mixture. Control treatments were placebo; morphine; fentanyl; bupivicaine; bupivicaine plus morphine plus saline; IV clonidine; IV clonidine plus IV patient controlled analgesia; or extradural sufentanil.

Participants included in the review

Patients who were undergoing the following types of surgery were included: thoracotomy; orthopaedic (including menisectomy); rectal or colorectal; abdominal; Caesarean section; abdominal aorta; total hip replacement; abdominal hysterectomy; scoliosis repair; intestinal resection or re-anastomosis; pancreatic; and abdominal.

Outcomes assessed in the review

The following outcomes were assessed: side-effects including hypotension, bradycardia, and sedation; pain intensity assessed using visual analogue score (VAS) alone or in combination with verbal scale. VAS was assessed only at rest, at rest and at cough, at rest and after mobilization, and at rest, at cough and after mobilization.

How were decisions on the relevance of primary studies made?

Each study was reviewed independently by two assessors who graded the studies into one of four categories. Only those classified as grade 1 (RCT with clearly defined objectives and adequate statistical analysis) were included in the review.

Assessment of study quality

The following criteria were used to assess validity: study design; and type of statistical tests and reasoning, number of patients excluded and lost for follow-up.Each study was reviewed independently by two assessors

Data extraction

Two assessors independently extracted the following data into data extraction forms: reference; main objective of study; type of study; population; type of anaesthesia; post-operative analgesia; analgesia efficacy assessment; side-effects assessment; and type of statistical tests and reasoning, number of patients excluded and lost to follow-up.

Methods of synthesis

How were the studies combined?

The studies were combined in a narrative review.

How were differences between studies investigated?

Comparisons were made on doses of clonidine, mode of administration, time of administration, type of anaesthesia and surgery, reference drug, assessment of pain intensity and relief, and timing of the assessment.

Results of the review

Sixteen studies met the inclusion criteria (681 patients).

There was a lack of at least two study designs enabling direct comparison. The authors found as many study designs as articles. When considering only one type of surgery, direct comparison between variables was not possible. The most serious shortcoming was the lack of a common background making meta-analysis impossible.

The main side effects recorded were hypotension, bradycardia and sedation.

Clonidine alone at a dose of 3 microgram/kg was found to be as efficacious as placebo in one study after thoracic surgery (one RCT with 20 patients). In orthopaedic and rectal surgery a lower dose (2 micrograms/kg) was found to be more efficacious than placebo (one RCT with 20 patients). In the remaining studies, the efficacy of clonidine was almost always superior to that of each drug alone.

Authors' conclusions

The data from the studies was difficult to interpret because of the tremendous variation in variables especially dose of clonidine, level of extradural injection, time of administration, type of anaesthesia, type of surgery, and reference and rescue drugs. The simultaneous extradural use of local anaesthetics and opiods further hindered data interpretation and precluded any meta-analysis.

CRD commentary

The aims and inclusion criteria were stated. Methods used to select primary studies and extract data were described. Relevant details of the included studies were clearly presented in tabular format. Given the heterogeneity among studies, a narrative review was appropriate. The discussion included consideration of the potential for publication bias.

It was not stated whether any language restrictions were applied to the included studies. The authors' conclusions were supported by the evidence.

Implications of the review for practice and research

Practice: The authors consider that the dose requirements to provide effective analgesia after a surgical procedure remain a matter of personal choice.

Research: The authors consider that well-designed adequately powered randomised controlled trials are required to determine the optimal dose regimen for post-operative pain. Future studies should clearly define and report the occurrence of side-effects and evaluate patient satisfaction.

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