Novel analgesic adjuncts for brachial plexus block: a systematic review
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Authors' objectives
To examine the analgesic effect of adding opioids, tramadol, clonidine and neostigmine to brachial plexus block.

Searching
Searches were conducted of MEDLINE (July 1966 to December 1999) and EMBASE (from 1980) using the following MeSH terms: "brachial plexus block" or "nerve block", 'clonidine', 'opioids', 'morphine', 'fentanyl', 'sufentanil', 'alfentanil', 'tramadol', and 'neostigmine'. Reference sections of eligible articles were examined. Abstracts, letters and nonpeer-reviewed publications were excluded.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled double-blind trials (RCTs) were included.

Specific interventions included in the review
The following analgesic adjuncts to local anaesthetic in brachial plexus block were included: opioids including morphine (0.75 to 100 micrograms/kg or 5 mg), fentanyl (75 micrograms), alfentanil (10 micrograms/kg), buprenorphine (3 micrograms/kg), butorphanol (83.3 micrograms/h), and sufentanil (0.2 micrograms/kg); clonidine (30 to 300 micrograms); and neostigmine (500 micrograms). Adjuncts were given intravenously or into brachial plexus infusions. Local anaesthetic agents included bupivacaine, lidocaine and mepivacaine either alone or in combination and both with or without epinephrine.

Participants included in the review
Adult patients undergoing brachial plexus block using the following approaches were included: axillary; supraclavicular; and interscalene.

Outcomes assessed in the review
The following measures of postoperative pain were assessed: visual analogue score (VAS); verbal response; time to first analgesic; and total analgesic consumption. Adverse reactions were assessed when these effects were statistically analysed. Studies assessing postoperative motor and sensory block without some assessment of pain were excluded.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Only double-blind RCTs were eligible. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The following data were independently extracted by the authors: author of study; year of publication; study design; presence of systemic control; adverse reactions; regional anaesthetic technique; concentrations and volume of local anaesthetic; type and dose of adjunct; and type of surgery. Each author independently reviewed each study using the above data.

Methods of synthesis
How were the studies combined?
Studies were grouped by intervention (opioids, clonidine and neostigmine) and combined in a narrative review.

How were differences between studies investigated?
Studies using a systemic control were considered separately from those using a systemic control. Studies were classified as supportive if the use of the adjunct demonstrated significant analgesic benefit versus the control and 'negative' if they did not.

Results of the review
Seventeen double-blind RCTs were included (796 patients).

Only two studies used more than twenty patients per group.

Opioids (10 RCTs).
Inconsistent results with six supportive RCTs and four negative RCTs. Some studies reported benefit on one dimension but not others.

Opioids with systemic control (four RCTs): inconsistent results with two supportive RCTs and two negative RCTs.

Opioids with no systemic control (six RCTs): inconsistent results with four supportive RCTs and two negative RCTs.

Nonopioid adjuncts.

1. Clonidine (six RCTs): Inconsistent results with five supportive RCTs and one negative RCT. Methodological flaws included small sample size and the use of non identical protocols.

Clonidine with systematic control (one RCT): supportive of clonidine adjunct.

Clonidine with no systemic control (five RCTs): inconsistent results with four supportive RCTs and one negative RCT.

2. Neostigmine (one RCT with no systemic control): supportive of neostigmine adjunct.

Adverse effects.
No serious adverse effects were mentioned in any of the studies. Nausea, vomiting and pruritus occurred both with peripheral and systemic administration of opioids.

Clonidine (six RCTs examined adverse reactions): side effects included mild sedation, bradycardia, hypotension, and decreased heart rate. Two RCTs included treatment arms given more than 150 micrograms of clonidine. One of these RCTs reported no difference in adverse reaction rates between 120 and 240 micrograms doses of clonidine and the other RCT noted hypotension only in those given 300 micrograms and none in those given 30 or 90 micrograms.

Authors' conclusions
Evidence regarding the analgesic benefits of opioid adjuncts remains equivocal and more evidence is required before their routine use can be recommended. Clonidine appears to have significant analgesic benefit and to cause minimal adverse effects when used in doses up to 150 micrograms. Data regarding other drugs, such as tramadol and neostigmine, are not sufficient to allow for any recommendations, and further studies are required.

CRD commentary
The aims were stated and inclusion criteria defined in terms of study design, interventions and outcome. Two databases were searched and details of the search reported. It was not stated whether any language restrictions were applied to the literature search and no attempt was made to locate unpublished studies thus raising the possibility of publication bias.
No details were given of methods used to select primary studies. Studies were limited to double-blind randomised controlled trials but no systematic assessment of validity was undertaken and methodological flaws in the primary studies were only mentioned briefly.

Some relevant detail of the primary studies was presented in tabular format but no details were given of participants, type of surgical operations performed, experience of anaesthetists or additional analgesia. Some studies reported significant benefit on one dimension but not on others and it was not clear how these studies were classified (supportive or negative). Potential causes of heterogeneity of results among studies were not discussed.

In view of the above limitations, the conclusion should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors report that evidence regarding the analgesic benefits of opioid adjuncts remains equivocal and that more evidence is required before their routine use can be recommended.

**Research:** The authors report that further randomised controlled clinical trials using a systematic control group with sufficient power to validate a negative result are required to examine the efficacy of using opioids, clonidine or neostigmine as an adjunct to local anaesthetic for brachial plexus block. The authors advise that such research should include an assessment of postoperative analgesia.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.