



EVIDENCE CENTRE REPORT

Can clonidine be used in effectively in epidural and intrathecal catheters?

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REQUEST:

Can clonidine be used in effectively in epidural and intrathecal catheters?

REQUESTED BY:

Mr. Elliot Rubenstein, Anaesthetist, Dandenong Hospital.

SUMMARY OF FINDINGS:

- The largest reported experience with clonidine for regional anaesthesia is with epidural administration.
- Published reports of epidural clonidine have been in the areas of chronic pain, intra- and post-operative pain, and in obstetric and paediatric populations. Chronic cancer and non-cancer pain studies are not examined in this report.
- The use of epidural clonidine as a supplement to general anaesthesia has been the subject of a number studies. Varying doses of clonidine showed a reduction in the utilisation of other agents such as propofol and fentanyl.
- In other studies, the safety and efficacy of epidural clonidine alone or in combination with opioids or local anaesthetics for post-operative analgesia has been examined. Many of the patients studied received either continuous epidural infusions or single or multiple boluses. Epidural clonidine clearly prolonged the analgesic effect and reduced the need for other agents.
- There has been no case of serious haemodynamic or respiratory depression in the epidural administration sample population.
- The addition of clonidine to intrathecal agents such as sufentanil and bupivacaine significantly increases the duration of analgesia with minimal haemodynamic changes.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines or health technology assessments, and randomised controlled trials. If we identify sound, relevant, material of this type the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable, or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details Of Evidence Request

Patients: patients with an epidural and/or intrathecal catheter

Interventions: clonidine

Comparisons: other agents

Outcomes: anaesthetic and analgesic effectiveness

Search terms

Catheter terms: epidural; epidural catheter; spinal block; spinal anaesthesia.

Drug terms: clonidine, pethidine, fentanyl, morphine; bupivacaine.

Resources Searched

We searched the following databases:

Cochrane Library CD-ROM

OVID Medline

NLM (PubMed)

CINAHL

Best Evidence

Effective Healthcare Bulletins

Sum Search

Society for Critical Care Medicine

Global Anesthesiology Server Network

Refinements, Searching & Reporting Constraints

We have included only English language articles published since 1997. Our electronic searching was performed during a one-week period: 7th – 14th February 2000.

Generally we search forward following a Level One study, however the meta-analysis by Armand et al (1998) was poorly done. This resulted in gathering studies from 1997 onwards. Furthermore, one study was examined for this report was published in 1995 but it was deemed relevant.

RESULTS:

From our sources we identified 17 articles which we categorised as follows:

Systematic reviews or meta-analyses	1
Evidence-based clinical practice guidelines	0
Randomised controlled trials	16
Controlled trials, cohort or case-control analytic studies	0
Descriptive case series	0
Consensus reports, non-evidence-based clinical practice guidelines	0
Narrative reviews	0
(add if appropriate) Economic studies	0

We are reasonably confident these articles represent the most important findings published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design with level of evidence available according to NHMRC guidelines (1998), patient description, scientific validity of the article, results and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

Findings

Epidural Administration:

According to Eisenach (1996) the systematic administration of α_2 adrenergic agonists have been advocated for pre-medication before surgery to provide sedation without respiratory depression. In the only study of pre-medication epidural clonidine by Penon et al (1991), 300mcg was administered to patients undergoing minor orthopaedic surgery. The study group observed intense sedation 60-120 minutes after injection in seven patients (total sample size = 15) accompanied by decreased blood pressure and heart rate. End tidal carbon dioxide (ETCO₂) and oxygen saturation (SaO₂) levels remained within normal limits.

The use of epidural clonidine as a supplement to general anaesthesia has been the subject of reports by De Kock (1999) and Murga (1994). In the double-blind study by De Kock (1999), an infusion of clonidine 6mg/kg/hr reduced intra-operative intravenous

propofol and post-operative analgesic requirements, with only minor alterations to heart rate (asymptomatic bradycardia). In the double-blind, placebo-controlled trial by Murga (1994), 300mcg epidural clonidine reduced intra-operative intravenous fentanyl requirements by 50% and provided post-operative analgesia for four hours without significantly reducing blood pressure. De Kock's earlier 1993 study also demonstrated that 8mcg/kg/hr of clonidine reduced total power of the electroencephalogram in anaesthetised women undergoing a vaginal hysterectomy. This same group demonstrated a 50-75% reduction in propofol and alfentanil use when clonidine was infused epidurally, compared with the same dose intravenously during surgery.

In seven studies, of which one was a meta-analysis, the safety and efficacy of epidural clonidine alone or in combination with opioids or local anaesthetics for post-operative analgesia were examined. The meta-analysis by Armand et al (1998) retrieved 16 articles but failed to perform odds ratios and/or weighted mean differences citing serious design flaws such as lack of controls and/or randomisation. Of the remaining individual studies, epidural clonidine clearly produced an analgesic effect, therefore reducing the need for other agents. The analgesic effect was recorded through visual analogue scales or defined as the time from epidural bolus clonidine administration until first request for pain medicine.

Side effects commonly observed after epidural clonidine in post-operative patients were hypotension, bradycardia and sedation (Paech et al 1997; Rockemann et al 1997; Senard et al 1998). The incidence of these side effects were similar between the three studies with all reporting a p value of <0.01 between the control and treatment arm. Claes et al (1998) reports similar haemodynamic events with a p value of 0.05. After bolus (Rockemann et al 1997) and epidural (Paech et al 1997; Senard et al 1998) administration, clonidine caused a dose dependent reduction in haemodynamic parameters such as blood pressure and heart rate. Agents used to restore haemodynamic instability were supplemental fluid administration, ephedrine and atropine. Sedation scores were comparable across all groups. None of the patients had evidence of respiratory depression by pulse oximetry (SaO₂) or arterial or ETCO₂.

Epidural clonidine has also been combined with other analgesics such as fentanyl, sufentanil and morphine and local anaesthetics such as bupivacaine for post-operative analgesia. Varying doses of clonidine increased the duration of analgesia resulting in better pain scale scores. In only one study (Rockemann et al 1997), epidural clonidine/morphine bolus resulted not only in inferior analgesia on post-operative days 1, 3 and 4 (p<0.017), but also more side effects compared with a mix of a bupivacaine/sufentanil epidural infusion.

Intrathecal Administration:

Only one study has tested the ability of variable doses of intrathecal clonidine (75, 150, 300 and 400mcg) alone to provide surgical anaesthesia (Malinovsky et al 1993). Like intrathecal opioids, large doses of clonidine are inadequate for surgical anaesthesia. For this reason, clonidine has been used as an adjunct to local anaesthetics rather than alone (Eisenach et al 1996).

Clonidine has been demonstrated repeatedly to prolong sensory and motor block from intrathecal local anaesthetics. For example, the study of 56 patients scheduled for a minor surgical procedure randomised to receive bupivacaine alone or with clonidine experienced 56% longer sensory and 68% longer motor block when clonidine was added (De Negri, 1997). Klimscha (1995) reports similar results with the addition of 150mcg of clonidine added to bupivacaine in 40 patients undergoing lower extremity orthopaedic surgery (p<0.05).

Of potential relevance to the combined spinal epidural technique to parturients, a combination of sufentanil with clonidine yielded 145 minutes of analgesia, without

adverse maternal or fetal effects, in comparison with 104 minutes of analgesia from sufentanil alone ($p < 0.05$) (Gautier, 1998). A similar study by D'Angelo (1999) also revealed a greater analgesic response from clonidine in combination with sufentanil and bupivacaine than sufentanil and bupivacaine alone (197 ± 70 vs. 132 ± 39 min; $p = 0.004$).

Benhamou et al (1998) also reports that post-operative analgesia was prolonged in women undergoing a caesarean section with intrathecal bupivacaine, clonidine and fentanyl combination versus bupivacaine alone or bupivacaine with clonidine ($p < 0.05$). Haemodynamic changes in blood pressure and heart rate were not significant in this group when compared with the other two combinations, bupivacaine alone and a concoction of bupivacaine, clonidine and fentanyl. Interestingly, Chiari et al (1999) reports changes in blood pressure and heart rate when higher doses of clonidine – 200mcg – were used as the sole analgesic agent during the first stage of labor.

Methodology

Randomisation

A valid clinical trial requires a method for assigning patients to a test or control treatment that is free of selection bias. The best method for ensuring a bias free selection is through a veritable randomisation technique. All of the studies evaluated in this report used a randomisation technique to assign patients to intervention groups. However, only studies by Benhamou et al (1998), D'Angelo et al (1999), Mercier et al (1998) and Paech et al (1997) described adequately their method of randomisation. Randomisation techniques included the blocked number sequence or a computer generated code. Most of the studies fail to mention allocation of concealment, inclusion of randomisation participants, masking and losses to follow up.

Similar Groups

The baseline characteristics of the test and control group must be more or less similar in order to provide a valid basis for comparison. Comparison for demographic variables such as age, gender, weight and height at baseline were assessed by all of the studies. Additional comparisons were made on epidural site and location, duration of operation and level of sensory and motor block.

Complete follow up of study subjects

Complete follow up of study subjects appeared to be fulfilled by all of the studies, although this was not specifically reported. Only one study (Rockemann et al 1997) reports the drop out rate in the given sample population. In the study by Brunswiler et al (1998) two patients in the placebo group, one in the morphine and three in the clonidine group noted – after 30 minutes of administration of intrathecal clonidine - the sensory level was $< L1$ and was therefore excluded from the calculation of the duration of the surgical anaesthesia.

Equal treatment of study subjects

To be able to attribute any differences in outcome to epidural or intrathecal clonidine, study subjects need to be treated equally. It would appear that from the review of studies that all patients were treated the same.

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

1. Armand, S. *et al.* Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task. *British Journal of Anaesthesia* **81**, 126-34 (1998).
2. Benhamou, D. *et al.* Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. *Anesthesia & Analgesia* **87**, 609-13 (1998).
3. De Kock, M., Wiederkehr, P., Laghmiche, A. & Scholtes, J. L. Epidural clonidine used as the sole analgesic agent during and after abdominal surgery. A dose-response study. *Anesthesiology* **86**, 285-92 (1997)
4. De Kock, M., Gautier, P., Pavlopoulou, A., Jonniaux, M. & Lavand'homme, P. Epidural clonidine or bupivacaine as the sole analgesic agent during and after abdominal surgery: a comparative study. *Anesthesiology* **90**, 1354-62 (1999)
5. De Negri, P. *et al.* Spinal anesthesia with clonidine and bupivacaine in young humans: interactions and effects on the cardiovascular system. *Minerva Anestesiologica* **63**, 119-25 (1997).
6. Senard, M. *et al.* Hemodynamic effects of epinephrine associated to an epidural clonidine-bupivacaine mixture during combined lumbar epidural and general anesthesia. *Acta Anaesthesiologica Belgica* **49**, 167-73 (1998)
7. Chiari, A. *et al.* Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor: a dose-response study. *Anesthesiology* **91**, 388-96 (1999)
8. Rockemann, M. G. *et al.* Epidural bolus clonidine/morphine versus epidural patient-controlled bupivacaine/sufentanil: quality of postoperative analgesia and cost-identification analysis. *Anesthesia & Analgesia* **85**, 864-9 (1997)
9. Paech, M. J., Pavy, T. J., Orlikowski, C. E., Lim, W. & Evans, S. F. Postoperative epidural infusion: a randomized, double-blind, dose-finding trial of clonidine in combination with bupivacaine and fentanyl. *Anesthesia & Analgesia* **84**, 1323-8 (1997).
10. Mercier, F. J. *et al.* The effect of adding a minidose of clonidine to intrathecal sufentanil for labor analgesia. *Anesthesiology* **89**, 594-601 (1998).
11. Gautier, P. E., De Kock, M., Fanard, L., Van Steenberge, A. & Hody, J. L. Intrathecal clonidine combined with sufentanil for labor analgesia [see comments]. *Anesthesiology* **88**, 651-6 (1998).
12. Klimscha, W. *et al.* Hemodynamic and analgesic effects of clonidine added repetitively to continuous epidural and spinal blocks. *Anesthesia & Analgesia* **80**, 322-7 (1995).
13. Murga, G., Samsó, E., Valles, J., Casanovas, P. & Puig, M. M. The effect of clonidine on intra-operative requirements of fentanyl during combined epidural/general anaesthesia. *Anaesthesia* **49**, 999-1002 (1994).

14. D'Angelo, R., Evans, E., Dean, L. A., Gaver, R. & Eisenach, J. C. Spinal clonidine prolongs labor analgesia from spinal sufentanil and bupivacaine. *Anesthesia & Analgesia* **88**, 573-6 (1999).
15. Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L. & Zbinden, A. M. Epidural epinephrine and clonidine: segmental analgesia and effects on different pain modalities. *Anesthesiology* **87**, 785-94 (1997).
16. Brunswiler, M., Van Gessel, E., Forster, A., Bruce, A. & Gamulin, Z. Comparison of clonidine, morphine or placebo mixed with bupivacaine during continuous spinal anaesthesia. *Canadian Journal of Anaesthesia* **45**, 735-40 (1998).

APPENDIX

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Levels Of Evidence

As Defined By "A Guide To The Development, Implementation And Evaluation Of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 1998):

Level I

Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.

Level II

Evidence obtained from at least one properly designed randomised controlled trials.

Level III

-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.

-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.

Level IV

Evidence obtained from case series (either post-test or pre-test and post-test), opinions of respected authorities (narrative reviews), descriptive studies, reports of expert (i.e. consensus) committees, case studies.

<p>Evidence Summary Systematic Review</p> <p>Epidural and Spinal Clonidine</p>	Armand et al 1998	Brunschwiler et al 1998	De Kock et al 1999
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	Level One	Level Two	Level Two
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Setting: Not stated. Number of Studies: The search retrieved 159 articles, of which 38 dealt with extradural clonidine, and 16 met the selection criteria. Participants: Those experiencing post-operative pain secondary to a surgical incision. Participant characteristics: Not stated. Outcome Measures: 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. Inclusion: Studies that were randomized, controlled, double-blind trials with clearly defined objectives and adequate statistical analysis. Exclusion criteria: Randomized trials lacking a control or blinding, those yielding questionable results or non-randomized, and studies consisting of non-randomized or non-controlled trials were excluded from this report.</p>	<p>Patients: Thirty-six geriatric patients undergoing elective knee replacement surgery under continuous spinal anaesthesia. Intervention: 2ml plain bupivacaine 0.5% and 0.15mg clonidine in 1ml. Comparison: 2ml bupivacaine 0.5% and 1ml NaCl 0.9% or 2ml bupivacaine 0.5% and 0.15mg Morphine. Outcomes: Levels of sensory block, degree of motor block, duration of surgical analgesia and duration of anaesthesia. Exclusion criteria: Not stated.</p>	<p>Patients: Sixty patients undergoing intestinal surgery during propofol anaesthesia. Intervention: Clonidine bolus of 10mg/kg followed by an infusion of 6mg/kg (group 1). Comparison: 7ml bupivacaine 0.5% bolus followed by an infusion of bupivacaine 0.25% at 7ml/hr (group 2) or 7ml bupivacaine 0.25% bolus followed by an infusion of bupivacaine 0.125% at 7ml/hr (group 3). Outcomes: Anaesthetic and analgesic effectiveness as measured by level of sensory block and patient sedation and visual pain scores. Exclusion criteria: Not stated.</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Search strategy: MEDLINE and Excerpta Medica were used to search for the studies. Keywords included regional analgesia, extradural clonidine, postoperative analgesia and postoperative pain. To avoid, the risk of overlooking any relevant articles, citations from articles were cross-referenced with those of the assessor's bibliography and those of the articles under review. Assessed validity: Unable to be assessed. Consistent results: No. Potential for bias: Ambiguous terms regarding the exclusion criteria such as 'clearly defined objectives' and 'adequate statistical analysis'.</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes. Patients treated equally: Yes. Potential for bias: Inadequate randomisation</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes. Patients treated equally: Yes. Potential for bias: Inadequate randomisation.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Because of the serious shortcomings of the 16 studies – different dosages, routes, additional analgesics and responses – a meta-analysis could not be applied.</p>	<p>Maximal sensory level and degree of motor block were comparable among the groups. Duration of surgical analgesia was 134±22 min and 163±48 min for the placebo and morphine groups respectively and 150 min for the clonidine group. The duration of anaesthesia was also comparable among the three groups: 218±47 min for the placebo group, 231±37 min for the morphine group and 231±48 min for the clonidine group.</p>	<p>During anaesthesia, group 1 patients required less propofol than those in groups 2 and 3 (p <0.05). Analgesia lasted 380 min (range, 180-645 min) in group 1 versus 30 min (range, 25-40 min) in group 2 and 22 min (range, 12.5-42 min) in group 3 (P <0.05). Sedation scores were significantly higher in group 1 during the first 2 hours post-operatively.</p>

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<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>The most serious shortcoming of all published studies dealing with postoperative extradural clonidine was the lack of a common background. Consequently, meta-analysis could not be applied to the selected trials.</p>	<p>In elderly patients 0.15mg clonidine but not 0.15mg morphine prolonged surgical analgesia when added to 10mg bupivacaine p.735.</p>	<p>Our results show that high doses of epidural clonidine potentiate general anaesthetics and provide more efficient post-operative analgesia than the two bupivacaine dosage regimens investigated p.1354.</p>
<p>REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions</p>	<p>The ambiguity of the inclusion and exclusion criteria begs to question the reliability of the search undertaken.</p>		

Evidence Summary Systematic Review <div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 10px auto;">Epidural and Spinal Clonidine</div>	Senard et al 1998	Benhamou et al 1998	Chiari et al 1999
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Level Two	Level Two	Level Two
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: Forty-four patients undergoing elective lumbar disc surgery under combined epidural and general anaesthesia.</p> <p>Intervention: 150mcg clonidine in bupivacaine 0.25% (group C).</p> <p>Comparison: 150mcg clonidine and 37.5 mcg epinephrine in bupivacaine 0.25% (group C+E).</p> <p>Outcomes: Haemodynamic parameters.</p> <p>Exclusion criteria: Patients with a history of cardiac disease, chronic hypertension or hemostasis disorder were not included.</p>	<p>Patients: Seventy-eight pregnant women at term undergoing elective caesarean section under spinal block.</p> <p>Intervention: Hyperbaric bupivacaine and 1 ml of saline (group B).</p> <p>Comparison: Hyperbaric bupivacaine with clonidine 75mcg and saline (group BC) or hyperbaric bupivacaine with fentanyl 12.5mcg and clonidine 75mcg (group BCF).</p> <p>Outcomes: Level of sensory and motor block.</p> <p>Exclusion criteria: Not stated.</p>	<p>Patients: Thirty-six parturients requesting labor analgesia.</p> <p>Intervention/Comparison: Administration of clonidine – 50, 100, or 200mcg.</p> <p>Outcomes: Visual analog pain score (VAPS), maternal haemodynamics, ephedrine requirements, sedation scores and fetal heart rate tracings.</p> <p>Exclusion criteria: Not stated.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Stated but evidence of the randomisation technique is not described.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate randomisation.</p>	<p>Randomisation: Yes, through the utilisation of a computer generated code.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate blinding an/or masking of sample population.</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate randomisation.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>Combined epidural and general anaesthesia induced a significant decrease in arterial pressure and heart rate in both groups ($P < 0.05$). SAP and MAP decreased significantly less in the patients receiving epinephrine ($p < 0.001$).</p>	<p>Intraoperatively, clonidine increased the spread of the sensory block and decreased pain (pain scores 23 ± 7 mm vs. 17 ± 6 and 2 ± 1 mm for group B versus group BC and group BCF; $p < 0.05$) and analgesic supplementation. This improved analgesia was best with the clonidine-fentanyl combination (group BC vs. group BCF; $p < 0.05$). Post-operative analgesia was prolonged only in group BCF ($p < 0.05$). Haemodynamic changes were not significantly different amongst the three groups.</p>	<p>Clonidine produced a reduction in VAPS with all three doses ($p < 0.001$). The duration of analgesia was significantly longer in patients receiving 200mcg (median, 143min; range, 75-210min) and 100 mcg (median, 118min; range, 60-180min) than 50mcg (median, 45min; 25-150min), and VAPS was lower in the 200mcg than in the 50mcg group. In the 200mcg, hypotension required significantly more often treatment with ephedrine than in the other groups. No adverse events or fetal heart rate abnormalities occurred.</p>
AUTHORS COMMENTS: Risk/benefit, limitations	<p>Low dose epidural epinephrine decreases arterial pressure instability during combined epidural and general anaesthesia p.167.</p>	<p>We conclude that adding a small dose of intrathecal clonidine to bupivacaine increases the quality of intraoperative analgesia and decreases pain during caesarean section. Combining clonidine with fentanyl further improved analgesia p.609.</p>	<p>In conclusion, 50-200mcg intrathecal clonidine produces a dose-dependent reduction in VAPS during the first stage of labour. Duration and quality of analgesia were more pronounced with 100mcg and 200mcg than with 50mcg, but 200mcg doses were also associated with a high incidence of hypotension. Further studies are warranted to evaluate the safety for the possible clinical use of intrathecal clonidine as the sole analgesic during labour p.395.</p>

<p>Evidence Summary Systematic Review</p> <p>Epidural and Spinal Clonidine</p>	Paech et al 1997	Rockemann et al 1997	De Kock et al 1997
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Level Two	Level Two	Level Two
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: One hundred and eighty women patients undergoing abdominal gynaecologic surgery under combined general and epidural anaesthesia.</p> <p>Intervention: 0.125% plain bupivacaine (Group C0) with fentanyl 2mcg/ml.</p> <p>Comparison: 0.125% plain bupivacaine with fentanyl 2mcg/ml and either 2mcg/ml (Group C10), 3mcg/ml (Group C15), or 4mcg/ml (Group C20) of clonidine.</p> <p>Outcomes: Minimise sedative and haemodynamic effects.</p> <p>Exclusion criteria: Exclusion criteria included pre-operative clonidine or opioid use or failure to establish epidural anaesthesia.</p>	<p>Patients: Sixty-eight patients undergoing pancreatic surgery under general anaesthesia.</p> <p>Intervention: Patient-controlled epidural application (PCEA) of 0.2ml/kg of a mixture of sufentanil 100mcg dissolved in bupivacaine 0.25%.</p> <p>Comparison: Epidural bolus of morphine 2mg and clonidine 150mcg/ in 10ml of NaCl 0.9% (BOLUS) on demand.</p> <p>Outcomes: Analgesia effectiveness at rest and movement, side effects, and costs of consumable items such as drugs, maintenance, and depreciation of the PCA device.</p> <p>Exclusion criteria: Exclusion criteria were age more than 65yr, chronic treatment with corticosteroids, allergy to one of the study substances, and contraindications to epidural puncture.</p>	<p>Patients: Fifty young adult patients undergoing intestinal resection for inflammatory bowel disease or second stage reanastomosis under general anaesthesia.</p> <p>Intervention/Comparison: Administration of clonidine of 2 (Group 1), 4 (Group 2), or 8 (Group 3)mcg/kg followed immediately by an infusion of 0.5, 1, or 2mcg/kg/hr.</p> <p>Outcomes: Sedation scores, level of sensory block and visual analog scales values at rest and at cough.</p> <p>Exclusion criteria: Exclusion criteria were chronic use of ant-inflammatory, cardiovascular, or psychotropic medication, including benzodiazepines; any renal or hepatic dysfunction; acute inflammatory bowel process at the time of surgery; inability to understand the study protocol; or a history of allergic reaction to any of the study drugs.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Yes, through the utilisation of a blocked random number sequence.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate blinding an/or masking of sample population.</p>	<p>Randomisation: Stated but evidence of randomisation technique is not described.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate randomisation</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate randomisation.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>Clonidine produced a dose-dependent improvement in analgesia at rest ($p=0.001$). Only the 4mcg/ml significantly increased the percentage of patients who experienced no pain with coughing (RR 1.4; 95% CI: 1.24-1.94), reduced pain scores with coughing ($p<0.05$) and significantly lowered supplementary fentanyl requirements ($p<0.05$). Clonidine produced a dose dependent decrease in blood pressure and pulse rate and an increase in vasopressor requirement ($p<0.01$).</p>	<p>Visual analog scales (VAS) score at rest and during coughing (3 ± 2.5 vs. 5 ± 3, $p<0.001$) was higher, and HR (79 ± 13 vs. 89 ± 15, $p<0.001$), and SAP (110 ± 18 vs. 124 ± 23, $p<0.001$) were lower, in the BOLUS compared with the PCEA group. The incidence of hypotension (SAP <80mmHg) was greater (6 vs. 0, $p<0.001$) in the BOLUS group. The incidence of all other side effects was comparable.</p>	<p>During surgery, 60% of the patients in Group 1 compared with 33% of patients in Group 2 and only 5% in Group 3 were removed from the study due to inadequate anaesthesia ($p<0.05$). Post-operatively, epidural clonidine provided complete analgesia lasting 30 ± 21min in Group 1 compared with 251 ± 237 min in group 2 or 369 ± 256 min in Group 3 ($p<0.05$ for Group 1 vs. Groups 2 and 3 and group 2 vs. Group 3).</p>
AUTHORS COMMENTS: Risk/benefit, limitations	<p>In conclusion, high quality analgesia after abdominal surgery produced by post-operative epidural bupivacaine and fentanyl was further enhanced by the addition of epidural clonidine at 4mcg/ml but not by lower dose rates p.1327.</p>	<p>We conclude that because of superior analgesia and reduced side effects at analogous costs, PCEA is preferable to the BOLUS technique for the treatment of post-operative pain p.864.</p>	<p>Our results show that the large dose of epidural clonidine used in this study can provide substantial intra and post-operative analgesia without any other analgesic. This study extends the observations made in human volunteers and women recovering from caesarean section delivery to patients undergoing major abdominal surgery p.291.</p>

<p>Evidence Summary Systematic Review</p> <p>Epidural and Spinal Clonidine</p>	D'Angelo et al 1998	Mercier et al 1998	Gautier et al 1998
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Level Two	Level Two	Level Two
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: Thirty parturients receiving combined spinal epidural analgesia.</p> <p>Intervention: Sufentanil 7.5mcg and bupivacaine 2.5mg with saline.</p> <p>Comparison: Sufentanil 7.5mcg and bupivacaine 2.5mg with saline and clonidine 50mcg.</p> <p>Outcomes: Sedation scores, level of sensory and motor block and haemodynamic parameters.</p> <p>Exclusion criteria: Not stated.</p>	<p>Patients: Fifty-three nulliparous women in painful labor receiving combined spinal epidural analgesia.</p> <p>Intervention: Intrathecal sufentanil 5mcg and clonidine 30mcg (SUF-CLO)</p> <p>Comparison: Sufentanil 5mcg and bupivacaine 5mg.</p> <p>Outcomes: The primary outcome was time until first request for additional analgesia.</p> <p>Exclusion criteria: Not stated.</p>	<p>Patients: Ninety-eight parturients requesting labor analgesia via combined spinal epidural technique.</p> <p>Intervention/Comparison: Administration of either 15mcgclonidine; 30mcg clonidine; 2.5mcg sufentanil; 5mcg sufentanil; 2.5mcg sufentanil and 15mcg clonidine; 2.5mcg sufentanil and 30mcg clonidine; 5mcg sufentanil and 15mcg clonidine; or 5mcg sufentanil and 30mcg clonidine.</p> <p>Outcomes: level of sensory and motor block visual analog scales values and incidence of nausea and pruritus.</p> <p>Exclusion criteria: Not stated.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Randomisation was performed with a computer-generated table of random numbers.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Self selected sample population.</p>	<p>Randomisation: Stated only with allocation of concealment. Generation of allocation not mentioned.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate randomisation.</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Potential for bias: Inadequate randomisation.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>The mean duration of analgesia was 132 ± 39 min for patients who received sufentanil and bupivacaine and 197 ± 70 min for those who received sufentanil, bupivacaine and clonidine (P=0.004). pain scores and side effects, including motor block, sedation, and hypotension, were similar between groups.</p>	<p>All parturients but one had effective analgesia in both groups, with similar sensory levels never exceeding T2. The duration (mean ± SD) of analgesia was longer in SFU-CLO group: 125 ±46 verses 97 ± 30min (p=0.007). The incidence of hypotension and the ephedrine requirements (median) were higher in the SFU-CLO group: 63% verses 12% (p<0.001) and 7.5mg verses 0mg (p<0.0001).</p>	<p>Patients receiving 30mcg intrathecal clonidine with 2.5 or 5mcg intrathecal sufentanil had significantly longer lasting analgesia (145 ± 36 and 145 ± 43mins vs. 104 ± 35 for those receiving intrathecal 5mcg sufentanil alone).</p>
AUTHORS COMMENTS: Risk/benefit, limitations	<p>We conclude that spinal clonidine 50mcg prolongs analgesia from spinal sufentanil 7.5mcg and bupivacaine 2.5mg without producing serious adverse side effects p.575.</p>	<p>The addition of 30mcg clonidine to 5mcg of intrathecal sufentanil extended the duration of labor analgesia without producing motor blockade. However, as previously reported with 100-200mcg clonidine, the incidence of hypotension and the ephedrine requirements were also increased, even when 30mcg clonidine only was added. .</p>	<p>Thirty micrograms of intrathecal clonidine combined with 2.5 or 5mcg intrathecal sufentanil significantly increased the duration of analgesia during the first stage of labor without adverse maternal or fetal effects p.651.</p>

<p>Evidence Summary Systematic Review</p> <p>Epidural and Spinal Clonidine</p>	<p>Curatolo et al 1997</p>	<p>DeNegri et al 1997</p>	<p>Murga et al 1994</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level Two</p>	<p>Level Two</p>	<p>Level Two</p>
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients: Fifteen healthy volunteers Intervention: Epinephrine 100mcg in saline. Comparison: Clonidine 8mcg/kg or NaCl 0.9% alone. Outcomes: Pain rating after electrical stimulation, pinprick, and cold perception on dermatome levels – S1, L4, L1, T9, T6, T1, and forehead. Exclusion criteria: Exclusion criteria were a history of alcohol abuse or intake of psychotropic drugs, the intake of opioids or nonsteroidal anti-inflammatory drugs in the past 2 weeks, the intake of other analgesics or sedatives in the past 24hours, coagulation abnormalities, pregnancy, or fever.</p>	<p>Patients: Fifty-six patients undergoing minor surgical procedure (spermatic vein ligation) under unilateral spinal anaesthesia. Intervention: 8mg of 1% hyperbaric bupivacaine plus clonidine 105mcg intrathecally. Comparison: 8mg of 1% hyperbaric bupivacaine plus NaCl 0.9%. Outcomes: Level of sensory and motor block, sedation level and haemodynamic parameters. Exclusion criteria: Not stated.</p>	<p>Patients: Forty patients undergoing abdominal hysterectomy under combined epidural and general anaesthesia. Intervention: Epidural clonidine 300mcg (Group 1) Comparison: Epidural saline placebo (Group 2) Outcomes: intra-operative fentanyl requirements, haemodynamic evaluation and analgesic effectiveness as measured by time to analgesia request and visual analogue scale scores. Exclusion criteria: Not stated.</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes. Patients treated equally: Yes. Potential for bias: Inadequate randomisation.</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes. Patients treated equally: Yes. Potential for bias: Inadequate randomisation.</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes. Patients treated equally: Yes. Potential for bias: Inadequate randomisation.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Epinephrine significantly reduced sensitivity to pinprick at L1-L4-S1. Clonidine significantly decreased pain rating after electrical stimulation at L1-L4 and sensitivity to pinprick and cold at L1-L4-S1, increased pressure pain tolerance threshold at S1.</p>	<p>In the clonidine treated group, no variations existed in cardiovascular parameters. Level of sensory/motor block, higher sedation level and significant post-operative analgesia was detected.</p>	<p>Mean (SD) intra-operative fentanyl requirements were 2.05 (0.18) and 3.66 (0.3) mcg/kg/hr for groups 1 and 2 respectively (P<0.001). Patients in Group 1 had a lower heart rate after tracheal intubation and surgical incision (p<0.02). In the recovery room, pain intensity was lower in Group 1 (p<0.003) and the mean (SD) time until analgesia request was increased from 48.5 (8.4) min in Group 2 to 235.7 (33.2) in Group 1 (P<0.001).</p>
<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>Epidural epinephrine and clonidine produce segmental hypoalgesia. Clonidine boluses should be administered at a spinal level corresponding to the painful area p.785.</p>	<p>In summary, the addition of clonidine to hyperbaric bupivacaine seems to be particularly useful in unilateral spinal anaesthesia, exerting minimal influence on haemodynamic parameters, and guaranteeing a satisfactory postoperative analgesia p.119.</p>	<p>Our results demonstrate that epidural clonidine produces decreased fentanyl requirements, improved cardiovascular stability, reduced pain intensity and effective post-operative analgesia in the recovery room p.999.</p>

<p>Evidence Summary Systematic Review</p> <p>Epidural and Spinal Clonidine</p>	<p>Klirmscha et al 1995</p>	<p>Claes et al 1998</p>	
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level Two</p>	<p>Level Two</p>	
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients: Forty patients scheduled for lower extremity orthopaedic surgery under continuous spinal or epidural anaesthesia. Intervention: Plain continuous spinal anaesthesia (CSA) or plain continuous epidural anaesthesia (CEA) Comparison: CSA with 150 mcg clonidine (CSA+C) or CEA with 150mcg clonidine (CEA+C). Outcomes: Haemodynamic and analgesic effects. Exclusion criteria: Exclusion criteria were a history of senile dementia and those with severe deformities of the spinal column.</p>	<p>Patients: One hundred healthy term parturients who requested epidural analgesia during childbirth. Intervention: Administration of 10ml bupivacaine 0.125% plus epinephrine 1:800,000 (Group BE) Comparison: Administration of 10ml bupivacaine 0.125% plus epinephrine 1:800,000 plus sufentanil 7.5mcg (Group BES) or clonidine 50mcg (Group BEC) or sufentanil 7.5mcg and clonidine 50mcg combined (Group BESC). Outcomes: Quality and duration of analgesia and the side effects induced by clonidine. Exclusion criteria: Parturients with an estimated fetal weight of less than 2500g were excluded from the study.</p>	<p>Patients: Intervention: Comparison: Outcomes: Exclusion criteria:</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes. Patients treated equally: Yes. Potential for bias: Inadequate randomisation.</p>	<p>Randomisation: Stated but evidence of the randomisation technique is not described. All patients accounted for: Yes Patients treated equally: Yes Potential for bias: Inadequate randomisation.</p>	<p>Randomisation: All patients accounted for: Patients treated equally: Potential for bias:</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Intrathecal, but not epidural, clonidine decreased MAP significantly compared with bupivacaine alone ($p<0.05$). MAP after intrathecal clonidine with bupivacaine was lower than epidural clonidine with bupivacaine 5 and 6 hours after injection. Duration of spinal and epidural anaesthesia was increased more than two fold by clonidine ($P<0.05$).</p>	<p>The overall quality and duration of analgesia were superior in the BESC group compared with the other groups ($p<0.05$). The frequency of side effects in the clonidine groups was comparable, with the exception of hypotension and sedation ($p<0.05$)</p>	
<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>In summary, the addition of clonidine prolongs analgesia by either route (p.322).</p>	<p>The addition of a low dose of clonidine to an epidural injection of bupivacaine with epinephrine and sufentanil provides better analgesia during labour, while keeping the side effects minimal and of minor clinical importance p.540.</p>	