Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer

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CRD summary
The authors concluded that neurolytic coeliac plexus blockade is safe and is associated with limited clinical reductions in pain, opioid consumption and constipation in patients with unresectable pancreatic cancer. The conclusions appear to reflect the limited evidence from a small number of studies, but poor reporting of review methods hinders an adequate assessment of the reliability of the results.

Authors' objectives
To compare the efficacy and safety of neurolytic coeliac plexus blockade (NCPB) with standard care for pain control in patients with unresectable pancreatic cancer.

Searching
MEDLINE (via PubMed), EMBASE, HealthSTAR and the Cochrane Library were searched from 1966 through August 2005 for studies published in full in English; the search terms were reported. In addition, the reference lists of included studies, selected studies and reviews were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared NCPB with standard treatment were eligible for inclusion. All but one of the included studies delivered NCPB using the classical posterior bilateral approach under radiological guidance; one study used an intraoperative approach. All studies used ethanol as the neurolytic agent and all control treatments included the standard use of non-steroidal anti-inflammatory drugs and morphine. Some studies included a sham procedure in the control treatment.

Participants included in the review
Studies of patients with unresectable pancreatic cancer were eligible for inclusion; studies of patients with other conditions were excluded. The mean age of the participants in the included studies was 61 years. The studies included patients with severe pain (though in one study not all patients had significant pre-treatment pain) with histologically proven unresectable pancreatic cancer at stages 3 or 4, ‘palliative’ or ‘advanced, palliative’. Some patients were in-patients and some were out-patients.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the outcomes. The primary review outcome was pain measured on a 10-point visual analogue scale (VAS). The secondary outcomes were daily opioid use (in mg of oral morphine-equivalents), adverse events, quality of life (QOL) and survival. Studies used different measures to evaluate QOL, including a multiscale and a uniscale QOL tool, an overall performance status tool and a standardised assessment tool (the Functional Assessment of Cancer Therapy-Pancreatic Cancer, FACT-PA).

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

Assessment of study quality
Study validity was assessed by classifying methods used for generating the allocation sequence, allocation concealment and blinding as adequate, inadequate or unclear. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved by discussion. Where possible, for
each study, outcomes data were extracted at baseline and 2, 4 and 8 weeks. Attempts were made to contact authors for missing data.

**Methods of synthesis**

How were the studies combined?

Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous data using the Mantel-Haenszel method, while pooled weighted mean differences (WMDs) and 95% CIs were calculated for continuous data using the inverse variance method. Fixed-effect models were used in the absence of significant statistical heterogeneity and random-effect models were used if heterogeneity was significant (chi-squared p<0.10 and I-squared >50%). A funnel plot was used to assess publication bias.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. For one study, subgroup analysis was used to examine the effects of NCPB only on patients who had significant pre-treatment pain (a VAS of 3 or more).

**Results of the review**

Five RCTs (n=302) were included.

Only one study was judged to be of adequate quality. Three studies were double-blinded and two were unblinded. Only one study described the method and generation of allocation concealment.

Pain control: the mean baseline VAS score was 5.0. The mean VAS pain score was statistically significantly lower in patients who received NCPB at 4 weeks (WMD -0.50, 95% CI: -0.85, -0.15, p=0.005; 3 studies, 117 patients) and at 8 weeks (WMD -0.60, 95% CI: -0.82, -0.37, p<0.0001; 4 studies, 204 patients) compared with the control group. The mean VAS pain score was also lower in patients who received NCPB after 2 weeks, but the difference was not statistically significant (random-effects WMD -0.34, 95% CI: 1.03, 0.34, p=0.33; 3 studies, 126 patients). A funnel plot at 8 weeks showed no asymmetry, suggesting the absence of publication bias.

Opioid use (3 studies): the mean daily opioid use was statistically significantly lower in patients who received NCPB at 2 weeks (WMD -39.99 mg, 95% CI: -60.08, -19.91, p<0.0001), 4 weeks (WMD -53.69, 95% CI: -79.65, -27.73, p<0.0001) and 8 weeks (WMD -80.45, 95% CI: -134.66, -26.24, p=0.0004) compared with the control group.

QOL: one study reported no significant difference in the FACT-PA between the NCPB and control groups. The other study reported no consistent differences between treatment groups.

Survival: there was no statistically significant difference in survival between the NCPB and control groups at 8 weeks (based on 4 studies).

Adverse events: the only significant difference in adverse events was a significant reduction in constipation in the NCPB group compared with the control group (RR 0.67, 95% CI: 0.49, 0.91, p=0.01).

**Authors’ conclusions**

NCPB is safe and is associated with limited clinical improvements in pain control, and reductions in opioid consumption and constipation compared with standard care, in patients with unresectable pancreatic cancer.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched but no attempts were made to minimise publication or language bias. The potential for publication bias was assessed but, since the number of studies was small, this was of limited value. Methods were used to minimise reviewer error and bias in the extraction of
data, but it was unclear whether similar steps were taken in the study selection or validity assessment processes. Some aspects of study quality were assessed and reported; the use of intention-to-treat analysis was not assessed, thus the effect of drop-outs on the results could not be evaluated.

Statistical heterogeneity was assessed and the data were generally appropriately pooled using meta-analysis. Most analyses were based on data from two or three studies, which restricts the strength of the evidence. The conclusions appear to reflect limited evidence from a small number of patients in a small number of studies, but incomplete reporting of review methods means it is not possible to adequately assess the reliability of the results.

Implications of the review for practice and research
Practice: The authors stated that NCPB may be used as an adjunctive treatment in selected patients with unresectable pancreatic cancer but it does not replace standard treatment for pain.

Research: The authors stated that future studies should be larger, randomise patients to an active versus a sham treatment, compare endoscopic ultrasound-guided NCPB with computed tomography-guided NCPB, and use a validated QOL measure as the primary outcome.

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