Continuous wound infiltration versus epidural analgesia after hepato-pancreato-biliary surgery (POP-UP): a randomised controlled, open-label, non-inferiority trial

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Summary

Background Epidural analgesia is the international standard for pain treatment in abdominal surgery. Although some studies have advocated continuous wound infiltration with local anaesthetics, robust evidence is lacking, especially on patient-reported outcome measures. We aimed to determine the effectiveness of continuous wound infiltration in hepato-pancreato-biliary surgery.

Methods In this randomised controlled, open label, non-inferiority trial (POP-UP), we enrolled adult patients undergoing hepato-pancreato-biliary surgery by subcostal or midline laparotomy in two Dutch hospitals. Patients were centrally randomised (1:1) to receive either pain treatment with continuous wound infiltration using bupivacaine plus patient-controlled analgesia with morphine or to receive (patient-controlled) epidural analgesia with bupivacaine and sufentanil. All patients were treated within an enhanced recovery setting. Randomisation was stratified by centre and type of incision. The primary outcome was the mean Overall Benefit of Analgesic Score (OBAS) from day 1–5, a validated composite endpoint of pain scores, opioid side-effects, and patient satisfaction (range 0 [best] to 28 [worst]). Analysis was per-protocol. The non-inferiority limit of the mean difference was +3·0. This trial is registered with the Netherlands Trial Registry, number NTR4948.

Findings Between Jan 20, 2015, and Sept 16, 2015, we randomly assigned 105 eligible patients: 53 to receive continuous wound infiltration and 52 to receive epidural analgesia. One patient in the continuous wound infiltration group discontinued treatment, as did five in the epidural analgesia group; of these five patients, preoperative placement failed in three (these patients were treated with continuous wound infiltration instead), one patient refused an epidural, and data for the primary endpoint was lost for one. Thus, 55 patients were included in the continuous wound infiltration group and 47 in the epidural analgesia group for the per-protocol analyses. Mean OBAS was 3·8 (SD 2·4) in the continuous wound infiltration group versus 4·4 (2·2) in the epidural group (mean difference –0·62, 95% CI –1·54 to 0·30). Because the upper bound of the one-sided 95% CI did not exceed +3·0, non-inferiority was shown. Four (7%) patients in the continuous wound infiltration group and five (11%) of those in the epidural group had an adverse event. One patient in the continuous wound infiltration group had a serious adverse event (temporary hypotension and arrhythmia after bolus injection); no serious adverse events were noted in the epidural group.

Interpretation These data suggest that continuous wound infiltration is non-inferior to epidural analgesia in hepato-pancreato-biliary surgery within an enhanced recovery setting. Further large-scale trials are required to make a definitive assessment of non-inferiority.

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Introduction

Prevention of postoperative pain is essential for the recovery of surgical patients. Epidural analgesia is currently the international standard for perioperative pain treatment in abdominal surgery.[1] The excellent analgesic effect of epidural analgesia is clearly established, but there are several potential disadvantages—eg, perioperative hypotension with the need to administer vasopressors; the risk of rare but serious neurological complications (epidural haematoma and abscess, with an incidence of one in 1000–6000 for thoracic epidurals[2–4]); failure rates in up to 30% of patients with periods of inadequate analgesia;[5] and need for preoperative placement in awake patients, considered as cumbersome by many patients, sometimes leading to refusal.[6,7]

Continuous wound infiltration with local anaesthetics has been suggested as an alternative for epidural analgesia for pain control after laparotomy. However, randomised trials including patient-reported outcome measures are currently lacking.[8] Standard pain scores do not take adverse effects into account and cannot explain variance in patients' satisfaction with pain therapy.[9] Additionally, intraoperative hypotension is associated with adverse outcomes such as acute kidney injury[10] and an increased 30-day mortality.[11] Finally, the current

Research in context

Evidence before this study

We did a systematic review in PubMed, Embase, and the Cochrane Library for studies concerning continuous wound infiltration and epidural analgesia in abdominal surgery published until Jan 1, 2016. The search terms used were "pain prevention", "epidural analgesia", "continuous wound infiltration", "wound catheters", and synonyms. The most relevant studies were two systematic reviews. The systematic review by Ventham and colleagues (2013) concluded that both methods provided a similar analgesic effect after abdominal surgery. Continuous wound infiltration proved to be a reliable alternative, with less urinary retention. When tested in an enhanced recovery setting, as Hughes and colleagues (2014) showed in their systematic review, epidural analgesia did not provide benefits for improved recovery or reduced morbidity. However, none of the included studies have integrated patient-reported outcomes in the primary endpoint.

Added value of this study

To the best of our knowledge, this is the first study comparing perioperative continuous wound infiltration and epidural analgesia using a validated instrument for the assessment of both pain control and patient-reported outcomes. Because of the reported need for trials about this subject in homogeneous patient populations, as expressed by the PROSPECT study group, we chose the field of hepato-pancreato-biliary surgery. This is a subspecialty wherein most procedures are done via laparotomy. All patients were treated according to the current clinical standards, including an enhanced recovery setting and perioperative goal-directed fluid therapy.

Implications of all the available evidence

When combining our findings with the available evidence, continuous wound infiltration could be considered to be non-inferior to epidural analgesia with regard to quality of analgesia and patient-reported outcome measures. This method, which is still relatively unknown and underused, thus might be regarded as a reliable alternative analgesic technique in abdominal surgery, although large-scale trials are needed for the definitive assessment of non-inferiority.

literature consists of relatively small trials, often with the use of suboptimal clinical standards in heterogeneous patient populations. We chose the field of hepato-pancreato-biliary surgery because the procedures are comparable in terms of length and location of incision. The aim of this study was to determine whether continuous wound infiltration is non-inferior to epidural analgesia using patient-reported outcome measures in a homogeneous patient population with optimal clinical standards.

Methods

Study design and participants

The POP-UP study was a two-centre, randomised controlled, open label, non-inferiority trial. The rationale and design of the trial have been described in detail elsewhere.[12]

Adults undergoing subcostal or midline laparotomy for hepato-pancreato-biliary indications at the Academic Medical Centre Amsterdam and the OLVG teaching hospital, Amsterdam, Netherlands, were eligible for inclusion. Patients were informed about the study at the outpatient department and were contacted afterwards by the study coordinator. All patients gave written informed consent. Patients were excluded if any of the following criteria were present: American Society of Anesthesiologists status of greater than 3, chronic opioid use (>1 year), renal failure (estimated glomerular filtration rate <40), contraindication for epidural analgesia, allergy for study medication, liver failure (Child-Pugh class C), or coagulopathies (international normalised ratio >1·5, partial thromboplastin time >1·5, platelets $<80\times10^9$ per L).

This study was investigator-initiated and investigator-driven and done in accordance with the principles of the Declaration of Helsinki.[13] The study was approved by the Medical Ethical Committee of the Academic Medical Centre Amsterdam (MEC2014_329). Secondary approval was obtained from the board of the OLVG teaching hospital, according to the Dutch CCMO External Review Directive 2012 (RET2012). A data monitoring safety board was not deemed necessary by the Medical Ethical Committee because of the estimated low study risk.

Randomisation and masking

Patients were randomly allocated (1:1) to continuous wound infiltration or epidural analgesia. Randomisation was done centrally using a web-based randomisation module and stratified according to centre and type of incision (subcostal *vs* midline). Computer-generated permutated block randomisation with a 1:1 allocation ratio and concealed varying permuted block sizes of two, four, six, and eight patients was used. Because of the invasive nature of the interventions, neither the trial participants nor the investigators were masked to group allocation.

Procedures

The procedures have previously been described.[12] Briefly, in the continuous wound infiltration group, patients received a total bolus injection of 30 mL bupivacaine 0·25% at the start of the procedure in the subfascial space (ie, between the peritoneum and the posterior fascia), the same plane wherein the catheter tip is placed at the end of the procedure (figure 1).

At the end of the operation, wound catheters were placed in the subfascial (ie, pre-peritoneal) space under direct vision. In case of subcostal incision (bilateral, extension to the right side) the first catheter was positioned in the right subcostal region, tunnelled via the rectus sheath to the