Double-blind randomized sham controlled trial of intraperitoneal bupivacaine during emergency laparoscopic cholecystectomy

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BACKGROUND: Intraperitoneal local anesthesia (IPLA) during elective laparoscopic cholecystectomy (el-LC) decreases post-operative pain. None of the studies have explored the efficacy of IPLA at emergency laparoscopic cholecystectomy (em-LC). A longer operative duration, the greater frequency of washing, and the inflammation associated with cholecystitis or pancreatitis are a few reasons why it cannot be assumed that a benefit in pain scores will be seen in em-LC with IPLA. This study was undertaken to assess the efficacy of IPLA in patients undergoing em-LC.

METHODS: Double-blind randomized sham controlled trial was conducted of 41 consecutive subjects undergoing em-LC. IPLA was delivered by a combination of injection to the diaphragmatic and topical wash over the liver and gallbladder with bupivacaine or saline. The primary outcome was visual analogue scale pain scores until discharge. Secondary outcomes included pain scores in theatre recovery and analgesic consumption.

RESULTS: One patient had a procedure converted to open and was excluded. There was no significant difference in pain scores in the ward or theatre recovery. Analgesic use, respiratory rate, oxygen saturation, duration to ambulation, eating, satisfaction scores, and time to discharge were comparable between the two groups.

CONCLUSIONS: IPLA during em-LC does not influence postoperative pain. Other modalities of analgesia should be explored for decreasing the interval between diagnosis of acute admission and em-LC.

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Introduction

To improve patient's experience after laparoscopic cholecystectomy (LC) and to drive day case surgery, efforts to decrease postoperative pain include the induction of intraperitoneal local anesthesia (IPLA). The majority of randomized trials to investigate the efficacy of IPLA demonstrate reduced pain scores in the treatment group. There are several trials, however, in which no reduction of pain is observed. Different local anesthesia (LA) agents, doses and mechanisms of administration may partly explain this variation. Shoulder pain is frequently experienced by patients and allegedly of diaphragmatic origin; LA wash over the liver and gallbladder has little impact upon this expression of pain. Diaphragmatic pain can be reduced by percutaneous injection and intraperitoneal arosol of LA. In a randomized trial comparing two different methods of IPLA with sham both direct injection of LA to the diaphragm and LA wash over the liver and gallbladder reduced postoperative pain in the immediate postoperative period. A prolonged duration of benefit was only observed in the group receiving diaphragmatic injection. Patients with cholecystitis or gallbladder stone pancreatitis benefit from LC during their emergency admission-emergency laparoscopic cholecystectomy (em-LC). Patients undergoing em-LC have an improvement in quality of life at one month compared to those who are treated with delayed LC and less time off work. This strategy reduces the risk of repeated admission with further pain or pancreatitis. The role of IPLA in patients undergoing em-LC is unknown with no data from randomized trials. This
study was undertaken to assess the efficacy of IPLA in patients undergoing em-LC.

Methods

This randomized prospective double blind sham-controlled trial was approved by the Warwickshire Research Ethics Committee, UK. Following trial commencement there were no changes to the study protocol or methods. Written informed consent was obtained prior to the procedure in each patient. Consecutive adult patients admitted with cholecystitis or gallbladder stone pancreatitis undergoing em-LC by one of two surgeons (RKJ or GJ) were eligible for inclusion to the trial. These two surgeons were responsible for participant enrolment. Cholecystitis was diagnosed with ultrasound confirmed gallbladder stones containing two of the following: an elevated neutrophil count (\(>7\times10^9/L\)), pyrexia greater than 38 °C or a thickened gallbladder wall on ultrasonography with pain induced by compression of the ultrasound probe on the gallbladder. Gallbladder stone pancreatitis was diagnosed in patients with a serum amylase level, greater than 3 times the upper limit of normal values (>303 U/L at our institution), with gallbladder stones seen on ultrasonography and cholangiographic evidence of common bile duct stones (endoscopic or magnetic resonance imaging). Patients undergoing elective laparoscopic cholecystectomy (el-LC) were not eligible for inclusion in the study. Patients converted to an open procedure were excluded after allocation and not included on an intention to treat analysis due to the pain that would be predicted from this procedure.

The study hypothesis was that the test treatment, IPLA, would produce similar pain relief in patients undergoing em-LC compared with those undergoing el-LC. In a previous RCT, both diaphragmatic injection and wash over the liver and gallbladder with bupivacaine were associated with decreased postoperative pain compared to sham group.\(^{[12]}\) LA was administered directly to the diaphragm and over the liver and gallbladder based upon the observed patterns of pain following LC.\(^{[12, 17, 20]}\) These studies demonstrate that pain arises from parietal, somatic and diaphragmatic sources. The studies were powered (see below) to detect the same difference between a previously validated technique and a control group.

Study design

There were two groups – a sham group that received sham injections/wash of 0.9% sodium chloride and a treatment group that received IPLA injections/wash of 0.25% bupivacaine. The trial technique of the wash/injection of sham or LA, randomization, blinding, surgical technique, anesthetic protocol and postoperative analgesia regimens were all the same as previously published in a trial of patients undergoing el-LC.\(^{[12]}\) Briefly, all patients received 20 mL of 0.25% bupivacaine to the port sites at the start of the operation. Intraoperatively prior to any dissection a topical wash of 10 mL LA or sham was administered over the anterior surface of the liver, gallbladder and porta hepatis. This was followed by subperitoneal injection into the right hemidiaphragm of 10 mL LA or sham. Randomization was performed by opening sealed sequential envelopes of a randomly generated sequence. Participants, surgeons (including those gathering data), ward nursing and medical staff were all blinded to the participants group allocation.

Outcome measures

The primary outcome measure was pain quantified by postoperative visual analogue scale (VAS, 0-100 mm) pain scores on arrival to the ward, at 4 and 8 hours after the end of the operation. Patients received an information sheet and verbal training in completing the pain scores in the morning of the procedure before sedation. Secondary outcome measures were a three point verbal rating scale (VRS, 0-3) pain score recorded in theatre recovery room at 1, 5, 10 minutes and then at 10-minute intervals following the procedure until transfer to the ward. Time to oral intake of food, ambulation and duration of stay were recorded. At discharge, subjects were asked how satisfied they were with the experience in general during the admission and specifically with postoperative pain (VAS 0-100 mm). There were no changes in trial outcomes after the start of the study.

Statistical analysis

Data were assessed for normality, and continuous variables are expressed as mean±SEM, geometric mean (95% confidence interval) or median (quartiles), as applicable. Comparisons of baseline demographic variables between the treatment groups were made by independent samples \(t\) test or Fisher's exact test for continuous and discrete variables, respectively. The preoperative VAS scores were subtracted from those taken at the ward and at 4 and 8 hours post procedure to calculate the change in the pain score brought about by the procedure. The resulting variables were compared between the sham and treatment groups using independent samples \(t\) test. VRS pain scores in theatre recovery were then compared using the Mann-Whitney test. Significance was accepted as \(P<0.05\). IBM SPSS 19 (IBM SPSS Inc.) was used to perform analyses.
The randomization sequence (computer generated) and sample size calculation were kindly provided by Dr N Parsons, medical statistician, University of Warwick, UK. The sample size calculation was performed at the 5% level with 80% power based upon a clinically important difference in pain severity of 13 mm. This has been reported previously between control and topical wash groups\cite{34,35} and corroborated by a meta-analysis\cite{36} which provides the best estimate of the standard deviation (18 mm). Based on this calculation, a total sample size of 30 patients per group was recommended to ensure that analyses were sufficiently powered.

**Results**

The trial had to be terminated early after an interim analysis demonstrating no difference between the trial groups. After the recruitment of 41 consecutive patients, em-LC was difficult to perform because of the change of theatre availability. A power calculation gave an expected power of 42.4% for the target sample size of 60 patients. This was largely due to the variability of the data that was greater than anticipated. Hence, the trial was terminated early because of futility. To this point, recruitment had been of consecutive patients agreeing to participate in the trial in a period of 50 weeks (June 2009-June 2010). One patient whose operation was converted to open was excluded after randomization (randomized to receive LA). The remaining patients completed the study (CONSORT diagram) (Fig. 1).

Patient age, gender, smoking habit, ethnic origin, and preoperative daily use of analgesics or antidepressants were comparable. No significant differences in operation duration, spillage of bile or blood, use of peritoneal irrigation or placement of a drain were observed between the groups (Table 1).

**Pain scores**

Before the operation there was no significant difference in VAS pain scores between the groups (sham: 8 [0-41], bupivacaine: 17 [4-20]; median [IQR]; \(P=0.380\)). Immediately after the operation there was no significant difference between the groups using a three-point VRS pain score measured at any time point (Fig. 2). In addition to this, no significant differences between the groups were detected in the increase of pain scores from the preoperative period to arrival at the ward (\(P=0.357\)), 4 and 8 hours after the operation (\(P=0.639\) and 0.849, respectively) or at discharge (\(P=0.772\)) (Fig. 3).

**Analgesic use**

No significant difference was seen in the total analgesic use in theatre recovery and in the ward after the operation and before discharge between the groups (\(P=0.879\)). The total number of doses received by each patient in the sham and treatment groups in the postoperative period was 7 (3-20) and 8 (2-15) respectively (median [IQR]). There was no significant difference in the use of opiate or non-opiate analgesics (data not shown) between the groups.

**Return of function, duration of stay and complications**

No difference was observed in the time to take
Peritoneal LA during acute cholecystectomy

Table 2. Summary of secondary outcome measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham</th>
<th>Bupivacaine</th>
<th>P value</th>
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<tr>
<td>Time to mobilize (h)</td>
<td>5.2 (4.4-10.5)</td>
<td>10.8 (4.5-12.7)</td>
<td>0.319</td>
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<td>Time to eat (h)</td>
<td>6.5 (4-11.8)</td>
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Values are median (interquartile range); the Mann-Whitney test.

Fig. 2. Three point VRS pain scores following arrival in theatre recovery. For each time point measured pain scores for the sham and treatment groups are presented with P values from the Mann-Whitney test. Bup: bupivacaine.

Fig. 3. Changes in VAS pain scores. Error bars represent SEM, and P values are from independent samples t test. Preop: preoperation; Postop: postoperation.

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d to a clinical examination by the anesthetist at the end of the operation. No evidence of pneumothorax was identified at this time or before discharge. Routine chest radiography showed no hemorrhage or hematoma in the patients after subperitoneal injection.

Discussion

In this study, we compared postoperative pain scores between patients receiving intra-portal delivery of LA and those receiving a sham treatment during em-LC. No significant effect was observed on pain scores, use of analgesic, or time to recovery. We used two techniques of IPLA: a topical wash (liver and gallbladder surface wash) which has been validated in several clinical trials[2-17] and a subperitoneal diaphragm injection. Previously we found diaphragmatic injection was effective, but not more than topical wash to reduce postoperative pain.[12] The techniques were combined to block visceral, parietal and diaphragmatic pain pathways. There are several explanations why no difference has been observed in the present study. First, the rate of wash was higher in this study than in previous studies, indicating the nature of em-LC. Topical LA was administered at the start of the procedure but not re-administered after wash in this study or previous studies. Topical wash provided at the end of the operation provides inferior analgesic benefit compared to insertion of the wash at the start of the operation.[4, 36] However, a wash would have no impact upon the diaphragmatic injection and is thus not the sole explanation. Second, inflammation associated with cholecystitis or pancreatitis may have reduced the effect of topical LA. Inflammatory mediators directly decrease the efficacy of LA in a pH dependent manner.[37, 38] Third, in the present study, 20 mL of 0.25% bupivacaine was divided in two 10 mL applications: one to wash over the liver and the second to inject the right diaphragm. In the previous study this same dose was administered either as a wash or diaphragmatic injection where both
were associated with a significant decrease in pain. It is possible that by keeping the dose the same but dividing it between two locations resulted in subtherapeutic levels of analgesic at both sites. Forth, preoperative pain scores were different between the groups in the present study and the previous study of subjects undergoing el-LC (18±4 in the present study compared to 6±2 in our previous study of patients undergoing el-LC;[12] mean±SEM) reflecting the presence of an acute inflammatory process in the emergency group.

In the case of pancreatitis, IPLA will have little or no effect on peripancreatic inflammation and in cholecystitis it may be that residual inflammatory mediators at the gallbladder bed, which would not have been exposed to LA at the time of wash, continue to be expressed after cholecystectomy. Diaphragmatic LA may be effective, but the overall pain experience for the patient may not be altered significantly.[5] A further difference is the nature of the patients' hospital experience which may affect their interpretation and expression of pain. Patients in an elective setting are admitted specifically to undergo LC. In the acute setting they are admitted primarily to treat cholecystitis or pancreatitis and when it is possible an em-LC is performed. For the majority of these patients, LC is not performed at the index admission.[39, 40] The availability of surgeons with suitable experience and theatre time appear to be the main influences on the rate of em-LC.[39, 41] Thus, in patients who do undergo em-LC there may be variable episodes of delay between consenting the patient for the procedure and when it has been performed, which may affect the expectations and experience of patients. In the present study, the median time from admission to LC was 3 days (range 0-7). The statistical power of the analysis may also have contributed to the non-significance of the difference between the treatment groups. This was lower than anticipated because of the combination of the standard deviation in the pain scores being higher than expected and the fact that the trial was terminated early. However, this trial was based upon data used for a randomized trial of bupivacaine versus sham in el-LC. In that study, two separate arms that used bupivacaine both demonstrated significantly lower pain scores versus sham. However, in this trial of IPLA at em-LC no difference was observed and thus we conclude that the addition of IPLA during em-LC is not beneficial.

The origins of pain after el-LC are multifactorial and include visceral pain from dissected peritoneum surrounding the gallbladder,[20] somatic pain from retained intraoperative blood or bile, insufflation of carbon dioxide with distension of the parietal peritoneum and with traumatic injury related to the trocars.[42] IPLA appears to be effective at el-LC; however, in the emergency setting it is not associated with a decrease in postoperative pain. Given the benefits of reduced hospital stay and reduced risk of further episodes of biliary colic, cholecystitis or pancreatitis[29, 30, 43] in performing LC at index admission for acute presentations of biliary disease, we suggest that efforts should be concentrated at increasing the proportion of those patients who undergo LC and at improving techniques of providing postoperative analgesia.

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Contributors: RKJ proposed the study, collected the data and drafted the paper. HJ analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. RKJ is the guarantor.

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Ethical approval: This study was approved by the Warwickshire Research Ethics Committee, United Kingdom and trial registration #: NCT01528722 www.clinicaltrials.gov.

Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References
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The purpose of knowledge is to liberate the person from restrictive limits while simultaneously maintain contact with the perceptible and ponderable universe.

―Wade Nobles