

## Continuous wound infusion of local anaesthetic agents following colorectal surgery: Systematic review and meta-analysis

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### Abstract

**AIM:** To provide a specific review and meta-analysis of the available evidence for continuous wound infusion of local anaesthetic agents following midline laparotomy for major colorectal surgery.

**METHODS:** Medline, Embase, trial registries, conference proceedings and article reference lists were searched to identify randomised, controlled trials of continuous wound infusion of local anaesthetic agents following colorectal surgery. The primary outcomes were opioid consumption, pain visual analogue scores (VASs), return to bowel function and length of hospital stay. Weighted mean difference were calculated for continuous outcomes.

**RESULTS:** Five trials containing 542 laparotomy wounds were eligible for inclusion. There was a significant decrease in post-operative pain VAS at rest on day 3 (weighted mean difference: -0.43; 95% CI: -0.81 to -0.04;  $P = 0.03$ ) but not on post-operative day 1 and 2. Local anaesthetic infusion was associated with a significant reduction in pain VAS on movement on all three post-operative days (day 1 weighted mean difference: -1.14; 95% CI: -2.24 to -0.041;  $P = 0.04$ , day 2 weighted mean difference: -0.97, 95% CI: -1.91

to -0.029;  $P = 0.04$ , day 3 weighted mean difference: -0.61; 95% CI: 1.01 to -0.20;  $P = 0.0038$ ). Local anaesthetic wound infusion was associated with a significant decrease in total opioid consumption (weighted mean difference: -40.13; 95% CI: -76.74 to -3.53;  $P = 0.03$ ). There was no significant decrease in length of stay (weighted mean difference: -20.87; 95% CI: -46.96 to 5.21;  $P = 0.12$ ) or return of bowel function (weighted mean difference: -9.40; 95% CI: -33.98 to 15.17;  $P = 0.45$ ).

**CONCLUSION:** The results of this systematic review and meta-analysis suggest that local anaesthetic wound infusion following laparotomy for major colorectal surgery is a promising technique but do not provide conclusive evidence of benefit. Further research is required including cost-effectiveness analysis.

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**Key words:** Colorectal surgery; Laparotomy; Local anaesthesia; Infusion; Wound healing

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### INTRODUCTION

Open surgery comprising colonic resection and primary bowel anastomosis accounts for up to a third of elective general surgical admissions<sup>[1]</sup>. The control of pain following these operations represents a major challenge as highly complex nociceptive pathways are involved<sup>[2-4]</sup>. Pain control following abdominal laparotomy and bowel anastomosis is therefore not amenable to

pharmacological monotherapy and modern analgesic strategies following major colorectal surgery involve the combination of many agents including parenteral opiates, nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and epidural infusion techniques<sup>[5]</sup>.

Unfortunately, there is no ideal analgesic regimen - all current techniques have disadvantages in the form of important side-effects, cost, patient compliance, procedural complications and delays in discharge<sup>[6]</sup>. Suboptimal post-operative pain control is of great clinical consequence and has been associated with cardiovascular and respiratory complications and increased gastrointestinal paralysis<sup>[5]</sup>.

A recent systematic review<sup>[7]</sup> has revealed the promise of continuous wound infusion of local anaesthetic agents to provide improved pain control following thoracic<sup>[8-10]</sup>, abdominal<sup>[11-13]</sup>, gynaecological<sup>[14-16]</sup>, and orthopaedic<sup>[17-19]</sup> operations, but there is a need for a more focused review of the evidence specific to colorectal laparotomy.

## MATERIALS AND METHODS

An electronic search was performed using the Embase and Medline databases from 1966 until 2007. The search terms "postoperative pain", "postoperative analgesia", "local anesthetics", "continuous", "infusion", "perfusion", "irrigation", "patient-controlled", and MeSH headings "Colorectal Surgery" (MeSH), "Laparotomy" (MeSH), were used in combination with the Boolean operators AND or OR. Two authors independently performed electronic searches in March 2008. The electronic search was supplemented by a hand search of published abstracts from meetings of the Surgical Research Society, the Society of Academic and Research Surgery, the American Society of Anesthesiologists, the Anaesthetic Research Society and the Association of Surgeons of Great Britain and Ireland from 1980 to 2007. The reference lists of articles obtained were also searched to identify further relevant citations. Finally, the search included the Current Controlled Trials Register ([www.controlled-trials.com](http://www.controlled-trials.com)) and the Cochrane Database of Controlled Trials.

Abstracts of the citations identified by the search were then scrutinised by two observers (SRW and AK) in order to determine eligibility for inclusion in the meta-analysis. Studies were included if they met each of the following criteria: randomised controlled trial, patients undergoing midline laparotomy for colorectal surgery, randomisation to groups with or without continuous wound infusion of local anaesthetic.

The primary outcome measure for the meta-analysis was the opioid consumption in each arm. Data from eligible trials were entered into a computerized spreadsheet for analysis. The quality of each trial was assessed using the Jadad scoring system<sup>[20]</sup>. The statistical analysis was performed using Statsdirect 2.5.7 (Statsdirect Ltd., UK). Weighted mean difference were calculated for the effect of local anaesthetic infusion on opioid consumption and linear analogue pain scores on post-operative days 1, 2

and 3. Further pooled outcome measures were duration of hospital stay and time to return of bowel function. All pooled outcome measures were determined using random-effects models as described by Der Simonian and Laird<sup>[21]</sup>. Heterogeneity amongst the trials was assessed by Cochran's Q statistic, a null hypothesis test in which  $P < 0.05$  is taken to indicate the presence of significant heterogeneity. The Egger test was used to assess the funnel plot for significant asymmetry, indicating possible publication or other biases.

## RESULTS

The initial search identified 590 papers. After screening, 5 randomised controlled trials were identified<sup>[22-26]</sup>. The five trials included 542 laparotomy wounds, of which 259 were randomised to infusion of local anaesthetic agents.

### Outcome measures

**Opioid consumption:** Four of the five trials reported total opioid consumption with or without local anaesthetic wound infusions<sup>[22-25]</sup> (Figure 1A). Local anaesthetic wound infusion was associated with a significant decrease in total opioid consumption (weighted mean difference: -40.13; 95% CI: -76.74 to -3.53;  $P = 0.03$ ). This outcome measure was associated with significant statistical heterogeneity (Cochran's  $Q = 45.31$ ,  $P = 0.02$ ) but not significant bias (Egger Test = -4.69,  $P = 0.27$ ).

Four of the five trials reported separate data for opioid consumption with or without local anaesthetic wound infusion on post-operative day 1<sup>[22,23,25,26]</sup> (Figure 1B). Local anaesthetic wound infusion was associated with a significant decrease in opioid consumption on post-operative day 1 (weighted mean difference: -8.34; 95% CI: -16.38 to -0.31;  $P = 0.04$ ). There was significant statistical heterogeneity (Cochran's  $Q = 9.98$ ,  $P = 0.019$ ) but not significant bias (Egger test: -2.11,  $P = 0.48$ ).

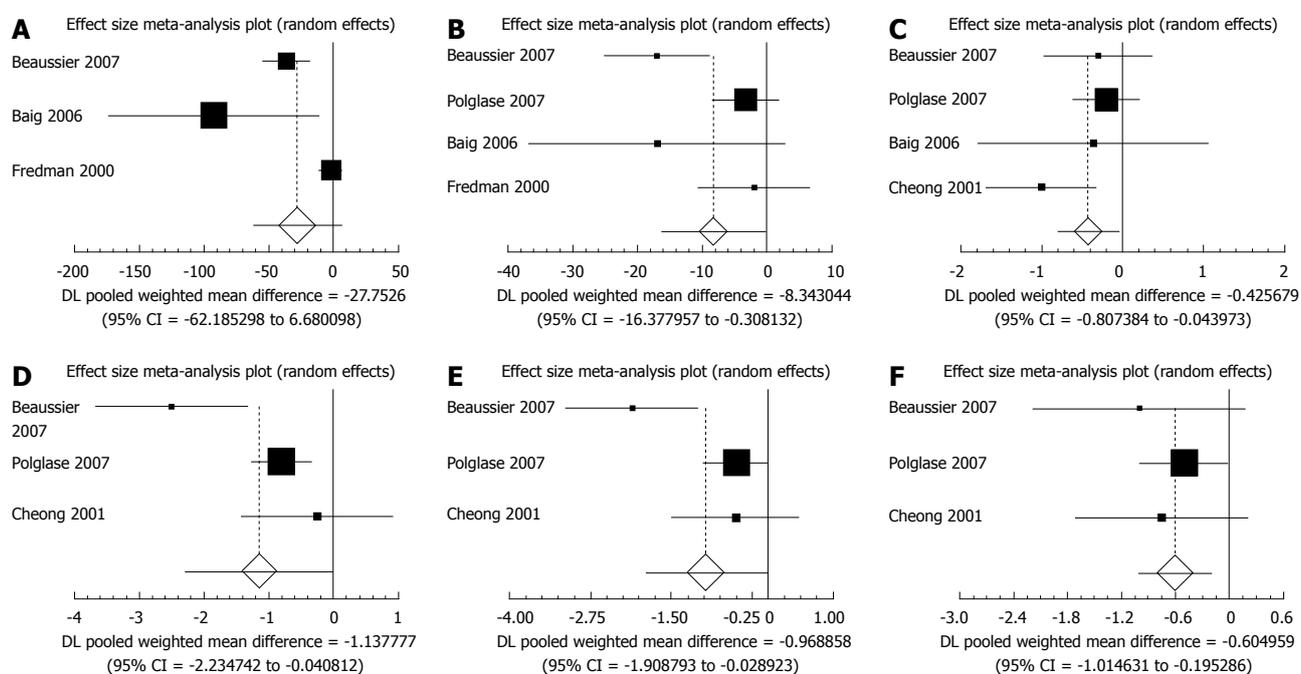
Three trials reported opioid consumption on post-operative days 2 and 3<sup>[22,25,26]</sup> (Table 1). There was no significant effect on opioid consumption (d 2 weighted mean difference: -9.49; 95% CI: -20.37 to 1.39;  $P = 0.087$ ; day 3 weighted mean difference: -4.80; 95% CI: -11.72 to 2.13;  $P = 0.17$ ). Two trials did not report this outcome measure rendering calculation of statistical heterogeneity or bias impossible.

### Visual analogue pain scores at rest

Four of the five trials reported visual analogue scores (VASs) of pain on post-operative days 1, 2 and 3<sup>[22-24,26]</sup>. Post-operative pain was reduced with local anaesthetic infusion on d 1 and 2 but the difference was not significant (Table 1) (d 1 weighted mean difference: -0.18; 95% CI: -1.31 to 0.95;  $P = 0.75$  and d 2 weighted mean difference: -0.20; 95% CI: -1.06 to 0.66;  $P = 0.65$ ). However, these outcome measures were associated with significant statistical heterogeneity (Cochran's  $Q = 18.15$  and  $15.42$ ,  $P < 0.05$ ). The use of local anaesthetic wound infusions was associated with a significant decrease in post-operative pain at rest on d 3 (Figure 1C) (weighted mean

Table 1 Results of meta-analyses

Outcome measure	Weighted mean difference	95% CI	P	Heterogeneity	Bias
Opioid consumption					
Total	-40.13	-76.74 to -3.53	0.03	$P = 0.02$	$P = 0.27$
Postoperative day 1	-8.34	-16.38 to -0.31	0.04	$P = 0.019$	$P = 0.48$
Postoperative day 2	-9.41	-20.37 to 1.39	0.087	NA	NA
Postoperative day 3	-4.8	-11.72 to 2.13	0.17	NA	NA
Visual analogue pain score at rest					
Postoperative day 1	-0.18	-1.31 to 0.95	0.75	$P < 0.05$	$P = 0.80$
Postoperative day 2	-0.20	-1.06 to 0.66	0.65	$P < 0.05$	$P = 0.47$
Postoperative day 3	-0.43	-0.81 to -0.044	0.029	NA	$P = 0.63$
Visual analogue pain score on coughing or movement					
Postoperative day 1	-1.14	-2.24 to -0.041	0.04	NA	NA
Postoperative day 2	-0.97	-1.91 to -0.029	0.04	NA	NA
Postoperative day 3	-0.61	1.01 to -0.20	0.0038	NA	NA
Duration of hospital stay	-20.87	-46.94 to 5.21	0.12	$P = 0.016$	$P = 0.30$
Time to return of bowel function	-9.4	-33.98 to 15.17	0.45	NA	NA



**Figure 1** A: Forest plot for total postoperative opioid consumption with or without continuous wound infusion of local anaesthetic agent; B: Forest plot for opioid consumption on postoperative d 1 with or without continuous wound infusion of local anaesthetic agent; C: Forest plot for pain VAS at rest on postoperative d 3 with or without continuous wound infusion of local anaesthetic agent; D: Forest plot for pain VAS on coughing or movement on postoperative d 1 with or without continuous wound infusion of local anaesthetic agent; E: Forest plot for pain VAS on coughing or movement on postoperative d 2 with or without continuous wound infusion of local anaesthetic agent; F: Forest plot for pain VAS on coughing or movement on postoperative d 3 with or without continuous wound infusion of local anaesthetic agent.

difference: -0.43; 95% CI: -0.81 to -0.044;  $P = 0.0288$ ). There was no evidence of bias for days 1, 2 or 3 (day 1 Egger test 0.99,  $P = 0.80$ ; day 2 Egger test 2.75,  $P = 0.47$ ; day 3 Egger test -1.00,  $P = 0.63$ ).

#### Visual analogue pain scores on coughing or movement

Three of the five trials reported pain VAS on coughing or movement, grouped for this analysis as a composite endpoint<sup>[23,24,26]</sup>. Local Anaesthetic infusion was associated with a significant reduction in pain VAS on all three post-operative days (Figures 1D to F) (day 1 weighted mean difference: -1.14; 95% CI: -2.24 to -0.041;  $P = 0.04$ , day 2 weighted mean difference: -0.97,

95% CI: -1.91 to -0.029;  $P = 0.04$ , day 3 weighted mean difference: -0.61; 95% CI: 1.01 to -0.20;  $P = 0.0038$ ). Two trials did not report this pain on movement, rendering calculation of statistical heterogeneity or bias impossible.

#### Duration of hospital stay

All five trials reported length of stay. There was no significant decrease in length of stay (Table 1) (weighted mean difference: -20.87; 95% CI: -46.96 to 5.21;  $P = 0.12$ ). This outcome measure was associated with significant statistical heterogeneity (Cochran's Q: 12.20,  $P = 0.016$ ) without significant bias (Egger test: -1.12,  $P = 0.30$ ).

### Time to return of bowel function

Mean time to production of faeces was reported by three trials<sup>[22-24]</sup>. There was no significant effect of local anaesthetic wound infusion (Table 1) (weighted mean difference: -9.40; 95% CI: -33.98 to 15.17;  $P = 0.45$ ). Two trials did not report this outcome measure rendering calculation of statistical heterogeneity or bias impossible.

## DISCUSSION

The results of our meta-analysis suggest that wound infusions are a promising adjunct to existing analgesic regimens following laparotomy for major colorectal surgery. The results do not, however, provide conclusive evidence of significant benefit conferred by this technique and it is doubtful whether the data gathered are sufficient to support generalisation of this conclusion to routine practice. The number of eligible trials (5) and total abdominal wounds (542) is small, and meta-analyses on small samples may be vulnerable to confounding if one or two of the eligible trials demonstrate a strong trend for or against the intervention under investigation.

For the purpose of this meta-analysis, the outcome measure "opioid consumption" was chosen to reflect opioid-sparing effect provided by local anaesthetic infusions. However, the significant statistical heterogeneity associated with this outcome measure reflects a variety of background analgesic regimens used in both control and treatment groups. Polglase *et al* utilized a multimodal analgesic regimen whereas the other trials studied used only patient controlled opioid analgesia to provide background analgesia. This degree of methodological heterogeneity between the trials may have influenced the meta-analysis.

Analysis of pain VAS may also have been affected by methodological heterogeneity between the trials studied. Furthermore, pain VAS is a non-parametric variable whereas the meta-analysis models used assume parametric distribution of the variables under study. The variable "length of stay" reflects a composite endpoint that may have been affected by several factors other than the presence of local anaesthetic infusions, and therefore it is not possible to draw causative inferences from the results of this pooled outcome measure with great validity. It was not possible to obtain sufficient data for all the trials under study to provide a reliable analysis of return to bowel function.

An economic analysis of local anaesthetic wound infusions is also needed - it seems likely that a greater amount of data is needed to clarify any trends in postoperative complications that may support the use of these infusions. Further large randomised controlled trials are required to investigate the promise of local anaesthetic wound infusions in major colorectal surgery, using standardized local anaesthetic agents, background analgesic regimens, experimental protocols, discharge criteria and anatomical site for wound infusion delivery.

In conclusion, Although suboptimal postoperative pain control is associated with cardiovascular, respira-

tory and gastrointestinal complications, many multimodal regimens for analgesia following major colorectal laparotomy provide inadequate pain relief. Although the number of trials available for meta-analysis is small, the available data demonstrate potential benefit in terms of reduction in opioid consumption following laparotomy for major colorectal surgery. Further large-scale studies will be needed to ascertain if any clear benefit or harm is conferred by the prophylactic use of local anaesthetic wound infusions in major colorectal surgery. Future research on this topic should also address the inaccuracies introduced by the methodological heterogeneity previously addressed in available trials, and provide a cost-effectiveness analysis of the use of continuous wound infusions in colorectal surgery.

## COMMENTS

### Background

Pain control following abdominal laparotomy and bowel anastomosis in colorectal surgery is a complex challenge not amenable to pharmacological monotherapy. Modern multimodal analgesic regimens may provide suboptimal postoperative pain control, which is associated with cardiovascular and respiratory complications and increased gastrointestinal paralysis.

### Research frontiers

Continuous wound infusions of local anaesthetic agents have been suggested to provide improved pain control following a broad range of surgical incisions, both alone and as part of a multimodal analgesic regimen.

### Innovations and breakthroughs

There is a need for a focused and quantitative review of the evidence for the analgesic benefit of continuous wound infusion of local anaesthetics specific to colorectal laparotomy, which is provided by this meta-analysis.

### Applications

The meta-analysis demonstrates potential benefit in terms of reduction in opioid consumption following laparotomy for major colorectal surgery. The review highlights the need for future research on this topic and identifies that such future research should address the inaccuracies introduced by the methodological heterogeneity identified in available trials, and provides a cost-effectiveness analysis of the use of continuous wound infusions in colorectal surgery.

### Terminology

Visual analogue scale (VAS) is a validated research tool used to quantitatively assess the subjective experience of patients' pain perception.

### Peer review

The authors present a systematic analysis of local anaesthetics in wounds after open colorectal surgery. This is an area that has not been addressed by systematic analysis previously. It is a well-done and timely review.

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