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SYSTEMATIC REVIEW

Analgesia for emergency laparotomy: a systematic review

Neha N Passi[1]

Aayushi Gupta[2]

Eimear Lusby[3]

Sara Scott[4]

Herman Sehmbi[5]

Sarah Hare[6]

Charles M Oliver[7,8]

Author details can be found at the end of this article

Correspondence to:
Neha N Passi; neha.passi@nhs.net

Abstract

Aims/Background Poorly controlled pain is common after emergency laparotomy. It causes distress, hinders rehabilitation, and predisposes to complications: prolonged hospitalisation, persistent pain, and reduced quality of life. The aim of this systematic review was to compare the relative efficacies of pre-emptive analgesia for emergency laparotomy to inform practice.

Methods We performed a search of MEDLINE, MEDLINE In-Process, Embase, PubMed, Web of Science and SCOPUS for comparator studies of preoperative/intraoperative interventions to control/reduce postoperative pain in adults undergoing emergency laparotomy (EL) for general surgical pathologies. Exclusion criteria: surgery including non-abdominal sites; postoperative sedation and/or intubation; non-formal assessment of pain; non-English manuscripts. All manuscripts were screened by two investigators.

Results We identified 2389 papers. Following handsearching and removal of duplicates, 1147 were screened. None were eligible for inclusion, with many looking at elective and/or laparoscopic surgeries.

Conclusion Our findings indicate there is no evidence base for pre-emptive analgesic strategies in emergency laparotomy. This contrasts substantially with elective cohorts. Potential reasons include variation in practice, management of physiological derangement taking priority, and perceived contraindications to neuraxial techniques. We urge a review of contemporary practice, with analysis of clinical data, to generate expert consensus.

Key words: Analgesia; Emergency laparotomy; Pre-emptive analgesia; Postoperative pain

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Background

Over 25,000 emergency laparotomies are performed annually in the UK for a wide range of intra-abdominal pathologies (NELA Project Team, 2020). Patients undergoing an emergency laparotomy (EL) represent a heterogenous group of high-risk patients who are predominantly present in the acute setting. Perioperative patient management is complex, necessitating control of systemic physiological disturbances and mitigation of pre-existing chronic morbidity and frailty, often with limited time for optimisation. The incidence of morbidity after EL is high and, for patients, is associated with prolonged hospital stays, reduced quality of life, physical function, and survival long after surgery (Kwong et al, 2018; NELA Project Team, 2018). For healthcare systems, the financial and resource implications of complicated postoperative recovery may be substantial and continue long after discharge from hospital (Bampoe et al, 2017). The identification of patient risk factors and perioperative processes of care associated with these adverse outcomes have therefore been the focus of intense scrutiny internationally (Vester-Andersen et al, 2014; Tengberg, Bay-Nielsen et al, 2017; NELA Project Team, 2018; NELA Project Team, 2020), and the resulting trials of pathways to facilitate routine delivery of selected processes have had some modest success (Huddart et al, 2015; Aggarwal et al, 2019; Peden et al, 2019).

Extensive literature from elective surgical populations demonstrates that acute post-surgical pain is common, with approximately a fifth of patients reporting severe pain at the surgical site in the first 24 hours after major elective surgery (PQIP team, 2021). Inadequate

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acute postoperative analgesia after elective laparotomy is associated with increased incidence of complications, reduced quality of recovery and rehabilitation in the short-term (Wu et al, 2005; Liu and Wu, 2007; Capdevila et al, 1999; van Boekel et al, 2019), as well as persistent post-surgical pain, lasting more than three months, and reduced quality of life in the months and years after surgery (Kehlet et al, 2006).

However, EL patients differ from those undergoing elective surgery in key areas. The development of pain in patients undergoing an emergency laparotomy may begin long before knife-to-skin, originating at the onset of the acute abdominal pathology and exacerbated by the ensuing systemic inflammatory response (Ilyas et al, 2019). Coupling this with the unpredictability of the surgical intervention to be delivered, adds a further complexity to identifying and delivering appropriate perioperative analgesic strategies for these patients (Foss, 2020). Indeed, limited data indicate that EL patients fare substantially worse than their elective counterparts, with 50% suffering moderate to severe pain immediately after surgery (Mrunalini et al, 2014; Bakshi et al, 2020), and PPSP affecting 19% (Tolstrup et al, 2019).

Prehabilitation for pain is slowly gaining traction and is being promoted by UK Faculty of Pain Medicine (Faculty of Pain Medicine of the Royal College of Anaesthetists, 2021; Srivastava et al, 2021). This encompasses three overall aspects: opioid de-prescribing, psychological preparation, and expectation management via patient education. Prehabilitation is feasible for elective abdominal surgery. By contrast, in EL there is a restricted window of opportunity for prehabilitation as surgery is time-critical. Ultimately a delicate balance lies between allowing for patient optimisation and proceeding to surgery. Additionally, EL often occurs out-of-hours when staffing is reduced and there is no capacity to deliver patient education. Also, the question remains as to whether a patient in pain, awaiting EL, would be receptive to receiving such information. Guidance advises to wean opiates preoperatively in patients undergoing elective surgery. Conversely, for a patient with an acute abdomen needing EL, escalating opiate requirements is likely to be necessary.

Analgesic interventions nestled within enhanced recovery pathways (ERP) are proposed to attenuate surgical stress responses, reduce complications, and improve postoperative recovery. Their routine use has delivered modest improvements in outcomes after elective abdominal surgery (Holte and Kehlet, 2002; Pöpping et al, 2008; Ljungqvist et al, 2017). Opioid-sparing techniques may confer additional benefits, reducing the cognitive dysfunction, respiratory depression, and gastrointestinal dysfunction that commonly accompany opioid use. ERPs incorporating proactive (rather than rescue) strategies for good postoperative pain control in EL might therefore be anticipated to deliver improvements in postoperative outcomes (Foss and Kehlet, 2020), but the lack of detail in the recently published EL-specific guidance, hints at a weak evidence base for specific analgesic strategies (Peden et al, 2021).

Our aims were therefore to identify and compare the relative efficacies of pre-emptive analgesia techniques in patients undergoing emergency laparotomy and identify the incidence of potentially attributable adverse events from the existing literature.

Methods

This manuscript was written to comply with PRISMA guidelines (please see **Supplementary File** for details) and was registered prospectively with International prospective register of systematic reviews (PROSPERO, registration number: CRD42019117460) (Moher et al, 2009). We intended to identify all studies of perioperative analgesia for emergency laparotomy using defined search terms. The types of study identified included randomised controlled trials, observational studies, and cohort studies.

We constructed search terms for each of Medline and Medline in-process, Embase, PubMed, Web of Science and SCOPUS. Table 1 displays the overall search terms used for the databases. Search terms used for specific search engines are reported in **Supplementary Tables 1–4.**

Eligibility criteria

Individuals over the age of 17 years undergoing emergency (urgent, emergency or immediately indicated) open laparotomy surgery for ‘general surgical’ pathologies and in

Table 1. Master spreadsheet of search protocols

Urgency	Surgery	Intervention	Outcome
immedia$ or urgen$ or unplan$ or emergen$ or expedited or acute$ or non elective or non-elective	laparotom$ or laparoscop$ or laparost$ or celiotom$ or abdomin$ or bowel or gastrointestinal or intestin$ or entero$ or enteric or esophagectom$ or gastrect$ or pancreatectom$ or $duodenectom$ or $jejunectom$ or cholecystectom$ or hepatectom$ or colorectal or colo-rectal or $colectom$ or hartmann$ or proctectom$ or adrenalectomy$ or splenectomy$ or volvulus or adhesiolysis or strictur$ or drain$ or evacuat$ or debride$ or explor$ or stoma or washout or herni$ or dissection or surgical hemostasis or exp Laparotomy/or exp Digestive System Surgical Procedures/	analgesi$ or manag$ or therap$ or control$ or relie$ or prevent$ or oral$ or parenteral$ or intravenous$ or transdermal$ or sublingual$ or opioid$ or opiate$ or an?esth$ or infiltrat$ or infus$ or catheter or wound or continuous or inject$ or block or neur?axial$ or regional$ or local$ or $peritone$ or $epidural$ or $spinal$ or intrathecal$ or transversus abdomin?s or TAP or rectus sheath or quadratus lumborum or QL or PCA or analgesia, patient?controlled or pain or lumb$ or thorac$	pain measur$ or pain severity or pain rating or pain grade pain score or pain assess$ or test or quantitativ$ or qualitativ$ or perception or visual analogue or VAS or NRS-101 or BS-11 or BRS-6 or VRS-4 or VRS-5 or Wong-Baker or Magill or Makowski or Comfort or colo?r analogue or Stanford or dynamic

whom the efficacy of any (two or more) pre-emptive pain management interventions, initiated in the preoperative or intraoperative period, were compared. Pre-emptive pain management interventions might include enteral, intravenous or topically applied medications (opioid, non-opioid, or adjunctive agents), wound infiltration, regional analgesia techniques and field blocks, neuraxial techniques and intravenous infusions (e.g. local anaesthetic). Unless analgesic elements were clearly defined, comparisons with 'usual practice' and 'general anaesthesia' were excluded.

Studies were excluded from the review if subjects were pregnant or non-human; manuscripts were not reported in English or were published before 1980; surgery included cardiac, obstetric, trauma, gynaecological, vascular or transplant procedures, non-abdominal sites or elective procedures; non-comparator studies, one or more analgesic interventions was exclusively postoperative (to exclude rescue analgesia), no formal assessment of pain scores or effectiveness of analgesia was recorded; and individuals who remained sedated and intubated over the period of the primary outcome.

Outcomes

Primary outcomes in this study were the incidence of moderate or severe pain at rest up to twenty-four hours after surgery, and time to mobilisation following surgery (Chiarotto et al, 2018). Secondary outcomes were morphine equivalent dose within 24 hours after surgery; incidence, grading and qualitative assessment of complications; and incidences of postoperative pulmonary complications, days alive out of hospital and time to flatus.

Screening and data extraction

Manuscripts were screened independently by two reviewers for eligibility and duplication. Screening was carried using defined inclusion and exclusion criteria as outlined above. Reasons for inclusion or exclusion were documented by each reviewer independently

using Google forms. In the event of any discrepancy between reviewers a third reviewer mediated consensus.

Data were to be extracted independently by two investigators using bespoke forms. In addition, each investigator would assess for risk of bias (for primary outcome) for each study using the Cochrane Collaboration's Risk of Bias Assessment Tool v2 (Sterne et al, 2019).

Data synthesis

Meta-analysis for included articles would have been conducted using pairwise meta-analysis in R-Studio (Version 1.1.453) and R (version 3.5.1). Heterogeneity would have been assessed using restricted maximum likelihood in the pair-wise meta-analysis, in addition to visually inspecting the forest plot for each pairwise comparison.

I^2 index and the chi-square statistic will have been computed within each pairwise comparison. If there was evidence of high heterogeneity, subgroup analyses or meta-regression would have been performed.

For the primary outcome, and key secondary outcomes, the strength of evidence pooled from the trials reviewed would be assessed using Grades of Recommendation, Assessment, Development, and Evaluation guidelines (Guyatt et al, 2011).

Results

Results of the search

Our database search yielded a total of 2389 results. The breakdown of results by the database is as follows: 493 in Medline and Medline in process, 520 in Embase, 534 in Pubmed, 443 in Web of Science 443 results and 399 in SCOPUS. After exclusion of duplicates 1147 candidate studies were identified. Two independent reviewers screened (titles, abstracts, and methods) each of the 1147 candidate manuscripts. None met our inclusion criteria (Figure 1) (Moher et al, 2009). More than 70% of the papers were excluded following a review of title and abstract, for non-eligible procedures or methods. For three titles, only a conference abstract was available, and the authors did not respond to requests for further information. The remaining studies were excluded on the grounds of study methods (placebo control or case report), cohort definition (inclusion of elective procedures) or surgical approach (laparoscopic).

We identified no other systematic review comparing the efficacies of perioperative analgesic modalities in cohorts of EL patients.

Included studies

No eligible studies were identified.

Excluded studies

Of the 1147 trial titles, abstracts and methods screened, none met our inclusion criteria.

A scoping review of funding platforms identified promising studies, including the Continuous rectus sheath Analgesia in eMErgency LaparOTomy trial (CAMELOT), but that again assesses a single modality (CAMELOT Trial, 2023).

Discussion

Having identified an unmet need, we have performed the first systematic review of the literature comparing efficacies of perioperative analgesic modalities in patients undergoing emergency general surgery via laparotomy. The key finding is that we identified no comparator studies that met our inclusion criteria. Furthermore, only a handful (<5) systematically assessed the efficacy of a single agent or modality in emergency laparotomy, and we identified no other systematic reviews comparing methods of pain control in this population.

A criticism of this systematic review is that it has not achieved its primary objective which was to identify the evidence base for analgesic perioperative strategies in the emergency laparotomy cohort. This could be attributed to our search strategy and its failure to identify

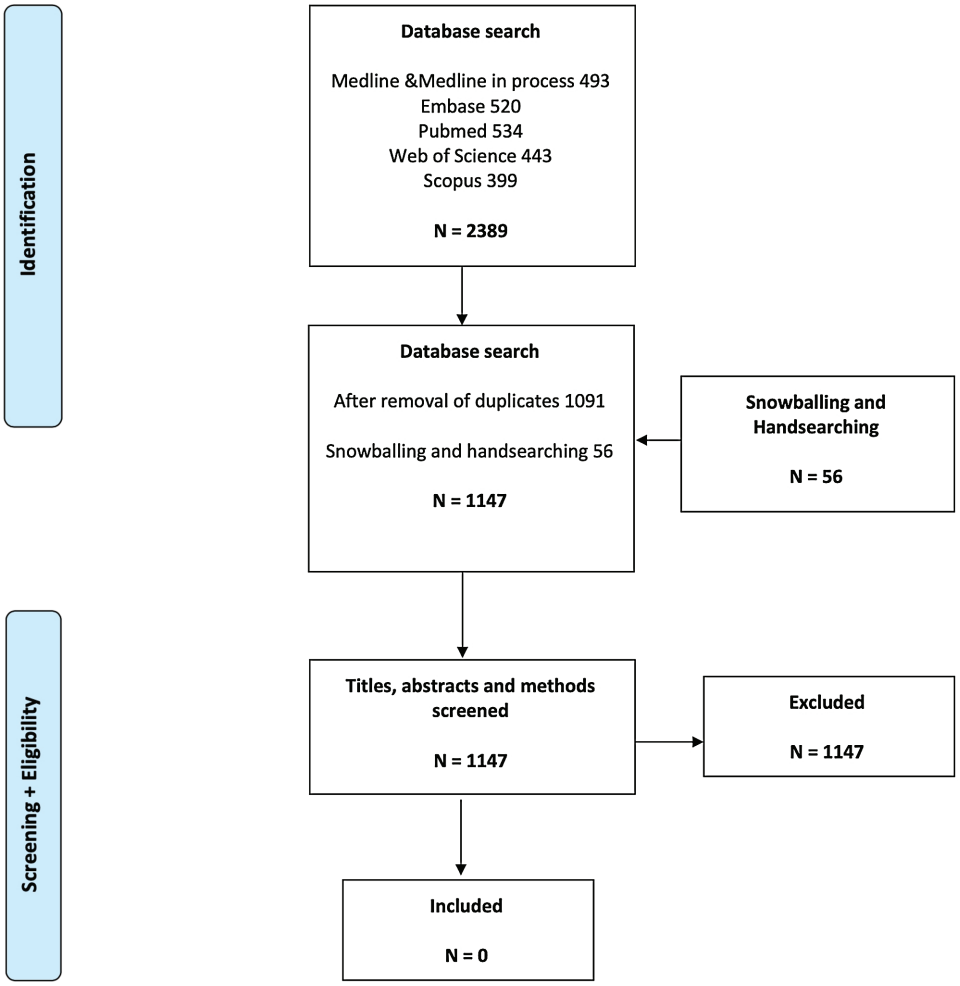

Figure 1. Search flow diagram (Adapted from: Moher et al, 2009).

all relevant papers. We believe that this is unlikely as our search methodology was robust. We did indeed identify studies which included emergency laparotomy patients, but these studies could not be included as they either looked at only single pain management intervention or were not randomised and/or comparator studies (Xin et al, 2017; Kılıç and Uğur, 2018). Furthermore, no previous systematic reviews or meta-analyses on this subject could be identified in the literature.

This absence of an evidence-base for pain interventions in EL contrasts with elective surgery, including intra-abdominal procedures. A recent systematic review looked at the efficacy of different analgesic modalities in patients undergoing an elective midline laparotomy. It revealed that epidural analgesia is superior in the early postoperative period (<24 hours) but is equal to other means of continuous analgesia (e.g. wound infiltration or abdominal wall blocks) at 48 hours (Howle et al, 2022). Whether these findings translate to the EL cohort remains to be seen.

The reasons to explain the current lack of clinical trials and the potential problems in designing future trials in EL are several-fold but can be considered in three categories: the emergency laparotomy patient, the multi-modal analgesic regimen and healthcare systems. Firstly, the emergency laparotomy patient is potentially septic and coagulopathic, which continues to fuel the debate over the appropriateness of neuraxial techniques; has limited potential for preoperative workup and consent; included disparate subgroups, most notably perforation vs obstruction; and diverse immediate postoperative trajectories, including induced coma, repeat surgery and high incidence of complications (Tengberg, Cihoric et al, 2017; Foss, 2020). The patient factor differences between the cohorts are arguably

the most pertinent and explain why simply extrapolating evidence from the elective work is fraught with error.

Secondly, while it is accepted that multi-modal analgesic regimens are best, defining the ideal multi-modal analgesic regimen requires consideration of all the systemic analgesic options given pre, intra and post-operatively. Unlike the elective cohort, this is likely to involve multiple teams, with initial treatment being initiated in A + E or on surgical wards and this too will be compounded by different patient factors. Defining an ideal multi-modal analgesic regimen while difficult is possible and systemic analgesic regimens are well-established components in ERP for patients undergoing elective surgery (Holte and Kehlet, 2002; Pöpping et al, 2008; Ljungqvist et al, 2017; Foss and Kehlet, 2020). Lastly, the healthcare systems in place used to assess and manage patients' pain post-operatively is again extremely heterogenous with a combination of nurse or physician led pain services using a variety of different pain measurement tools and at different time points.

Conclusion

Inadequate postoperative pain control is common, predisposes to multisystem complications and persistent post-surgical pain, and impairs recovery and rehabilitation. This systematic review of the literature demonstrates that there is no current evidence base on which to determine the ideal pre-emptive analgesic strategies in patients undergoing emergency laparotomy. We have considered both the reasons to explain these findings and recognise the challenges in designing trials in the emergency laparotomy cohort.

Given the equipoise that exists, there are opportunities both for targeted randomised control trials to compare specific modalities in EL and observational analyses harnessing existing data collection platforms in EL. With this evidence base, it will then be possible to promote the move from existing 'rescue' models for perioperative analgesia in EL to pre-emptive, patient-centric interventions that are nestled within ERP. Knowledge of risk factors for and the incidence of complications due to these interventions will inform patient choice. Achieving this requires us to first address the urgent need for research in this area as highlighted by this systematic review.

Key points

- Poorly controlled pain following emergency laparotomy is associated with complications, increased morbidity, and patient distress
- Our systematic review of the literature shows there is currently no evidence base for pre-emptive analgesic strategies in emergency laparotomies, especially compared to elective
- This is probably multifactorial in origin: variations in practice, physiological derangement taking priority over analgesia, perceived contraindications to neuraxial techniques in this cohort
- Future work must establish expert consensus to inform practice, by reviewing contemporary practice and analysing retrospective and prospective clinical data

Author details

[1]Department of Anaesthesia, Whipps Cross Hospital, London, UK

[2]Department of Anaesthesia, Royal Free Hospital, London, UK

[3]Department of Anaesthesia, University Hospitals Sussex NHS Foundation Trust, Brighton, UK

[4]Department of Anaesthesia, Queen Elizabeth Hospital, Gateshead, UK

[5]London Health Sciences Centre, Western University, London, Canada

[6]Department of Anaesthesia, Medway Maritime Hospital, Gillingham, Kent, UK

[7]Centre for Perioperative Medicine, University College London, London, UK

[8]Department of Anaesthesia, University College London Hospital, London, UK

Availability of data and materials

All derived materials are included in the manuscript and supplementary files.

Ethics approval and consent to participate

Not applicable.

Author contributions

NNP and AG are joint first authors. NNP drafted the manuscript. NNP, SH, HS, AG and CMO designed the research study. NNP, SS, EL and CMO performed the research. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of interest

SH and CMO have worked on the National Emergency Laparotomy Audit (NELA) project team. The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2023.0409.

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