




BMJ Open Intrathecal diamorphine for perioperative analgesia during colorectal surgery: a cross-sectional survey of current UK practice

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ABSTRACT

Objectives To describe current UK clinical practice around the use of intrathecal diamorphine as analgesia for major elective laparoscopic colorectal surgery.

Design Online self-administered survey.

Setting Acute public hospitals in the UK (National Health Service – NHS).

Participants Consultant anaesthetists involved in colorectal surgery lists.

Main outcome measures Rate of intrathecal opioids used by anaesthetists for elective laparoscopic colorectal procedures; minimum, most common and maximum doses of intrathecal diamorphine used, timing of administration of intrathecal injection, and relationship between the number of patients anaesthetised for laparoscopic colorectal resections per month by each anaesthetist, and the doses of intrathecal diamorphine they administer.

Results In total, 479 responses were received. Of these, 399 (83%) use intrathecal opioid routinely: 351/399 (88%) use diamorphine, 35 (8.8%) use morphine, 8 (2%) use fentanyl, and 7 (1.3%) use other drugs. The median intrathecal diamorphine dose most commonly administered by anaesthetists was 500 µg (IQR 400–750 [(range 200–1500)]). The median of the maximum dose administered by anaesthetists was 600 µg (IQR 500–1000 [(range 200–2000)]). Greater intrathecal diamorphine dosing was positively associated with higher number of cases per month ($\rho=0.113$, $pp=0.033$).

Conclusions Intrathecal diamorphine is widely used by UK anaesthetists for patients undergoing major elective laparoscopic colorectal surgery. However, there is little consensus regarding optimal dosing. Therefore, high-quality randomised dose-response trials are needed to investigate the relationship between doses of intrathecal diamorphine and patient outcomes.

INTRODUCTION

Adequate control of postoperative pain after colorectal surgery is a key factor in improving recovery and outcomes for patients, as detailed in Enhanced Recovery After Surgery (ERAS) guidelines.¹ Commonly used analgesic techniques used by anaesthetists include epidural (thoracic or lumbar), intravenous

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study reports doses of intrathecal (spinal) diamorphine most commonly used by anaesthetists for patients undergoing elective major laparoscopic colorectal surgery.
- ⇒ Anaesthetists working at a large number of public hospitals in the UK were invited to complete an online questionnaire asking about the doses of intrathecal diamorphine they use for certain named surgical procedures, as well as other analgesic options offered.
- ⇒ Patient outcomes and adverse events following different intrathecal diamorphine doses cannot be accurately assessed by this cross-sectional study and are not reported.

lidocaine, intraperitoneal local anaesthetics and spinal anaesthesia.^{2–5} Alongside perioperative analgesia, a minimally invasive laparoscopic surgical approach is associated with earlier recovery and reduced risk of perioperative complications.⁶ Infusion of local anaesthetic with or without opiate into the thoracic epidural space (thoracic epidural analgesia (TEA)) remains the gold standard for patients undergoing open colorectal surgery in current ERAS guidelines.^{1,7} However, more recent evidence suggests benefits of TEA over other modes of analgesia have been overstated and that TEA may worsen certain outcomes, including increased high dependency unit length of stay.⁸

Intrathecal diamorphine (diacetylmorphine in the USA; ITD) with or without local anaesthetic is an alternative to TEA, which may avoid limb and girdle weakness (causing immobility) and sympathetic blockade (causing hypotension), which are two common complications with TEA that may worsen patients' outcomes. Furthermore, absence of an indwelling epidural catheter and use of smaller gauge atraumatic needles

are purported to reduce infective and traumatic complications respectively.⁹ Diamorphine is a semisynthetic, lipophilic prodrug, which is twice as potent and 280 times more lipid soluble than morphine.¹⁰ It is deacetylated by the liver into its active metabolites (morphine and 6 mono-acetyl morphine), which act at opioid receptors in the dorsal horns of the spinal cord. ITD provides effective postoperative analgesia^{9 11} and may be combined with local anaesthetic to provide anaesthesia. Given the proximity of the drug to its zone of action, a lower intrathecal opiate dose is required to achieve adequate analgesia when compared with oral or parenteral administration, reducing the risk of side effects.¹² In the context of colorectal surgery, excessive opioid dosing is associated with sedation, nausea and ileus, all of which may be less pronounced with intrathecally administered opioids.^{13–15}

Despite the potential benefits of ITD versus opioids delivered via other routes, there is no consensus on the optimal intrathecal dose that may produce better quality of postoperative pain control. We conducted a self-administered survey of anaesthetists involved in the management of laparoscopic colorectal surgeries across the UK. The aim of this survey was to establish the dose of ITD used by consultant anaesthetists in the UK.

METHODS

A self-administered survey of anaesthetists involved in the management of colorectal surgeries was conducted across UK. Lists of UK public hospitals were obtained from English,¹⁶ Welsh,¹⁷ Scottish¹⁸ and Northern Irish¹⁹ National Health Service (NHS) webpages. From these lists, we excluded all the hospitals that do not provide surgical services (eg, community and mental health hospitals and rehabilitation centres), maternity centres, single-specialty hospitals (eg, eye hospitals, heart and lung centres, neuroscience hospitals and orthopaedic hospitals) and those hospitals that did not have an anaesthetic department or were not contactable. The anaesthetic departments of 138 acute NHS hospitals were eventually contacted, either by phone or email. Of these, 97 (70%) agreed to distribute an email invitation to their consultants to complete an electronic form of the survey. The survey was distributed between 10 February and 13 May 2019.

Recent methodological recommendations for self-administered surveys were used for the development of the questionnaire.²⁰ A pilot survey was developed and tested by consultant anaesthetists at our institution to evaluate the instrument length and logic. Following this, feedback was used to produce an improved online survey with the SurveyMonkey online platform to assess anaesthetists' practice regarding postoperative analgesia for patients undergoing laparoscopic colorectal surgery (online supplemental data). Respondents were asked about their specialty grade and the average number of patients they anaesthetise for laparoscopic colorectal resections per month. They were also asked about the

mode of postoperative analgesia they usually provide for specified commonly performed laparoscopic procedures: right hemicolectomy, left hemicolectomy, anterior resection, abdominoperineal resection and transanal total mesorectal excision. For each type of surgery, they were asked about the primary mode of analgesia they administer: intrathecal opioid, lumbar epidural analgesia, TEA, combined spinal epidural, patient controlled analgesia, transversus abdominis plane block, lidocaine infusion or simple analgesia (principally paracetamol, non-steroidal anti-inflammatory drugs and/or opioids when required). Respondents who used intrathecal opioid were asked about the drug(s) they usually administer intrathecally, including minimum, maximum and most common doses. Finally, they were asked if they administered intrathecal opioid prior to, or following, the induction of general anaesthesia or at the end of surgery, and whether this decision was affected by predicted surgical duration.

Patient and public involvement was not sought for this study, as the subjects of the study were health professionals (rather than the public).

Data distributions were checked for normality with Shapiro-Wilk normality tests. For categorical (including ordinal) data, frequencies were calculated and are presented as percentage of total, with differences tested using χ^2 tests. Non-parametric continuous data are reported as medians (IQR (range)). Ninety-five per cent CIs are not reported, as the sample size is unknown and cannot be reliably estimated. Spearman's rho was used to determine the degree of correlation between the number of patients anaesthetised per month and the dose of ITD. There were no missing data. A p value of <0.05 was considered statistically significant. All analyses were carried out (and figures produced) using R V.4.0.2 for Mac and the packages 'ggplot2' and 'patchwork'.^{21–23} The primary outcome was the rate of intrathecal diamorphine used by anaesthetists for elective laparoscopic colorectal procedures. Secondary outcomes were doses of diamorphine used and timing of administration.

RESULTS

In total, responses were received from 479 consultant anaesthetists spanning 97 NHS Trusts in the UK.

Most anaesthetists (399 of 479, 83.3%) used intrathecal opioid for at least one type of colorectal surgery: 61.6% for right hemicolectomy, 65.1% for left hemicolectomy (including sigmoidectomy), 63.7% for anterior resection, 54.5% for abdominoperineal resection (including extralevator abdominoperineal excision) and 52% for transanal total mesorectal excision (table 1).

Out of 399 respondents who routinely administer intrathecal opioid, 351 (88%) use diamorphine, 35 (8.8%) use morphine, 8 (2%) use fentanyl, 2 (0.5%) and 7 (1.3%) use other drugs. Two respondents (0.5%) use local anaesthetic only with no opioid.

The median intrathecal diamorphine dose usually administered by anaesthetists was 500 µg (IQR 400–750

Table 1 Primary modes of analgesia used by consultant anaesthetists (n=479) for various laparoscopic colorectal resections

	Spinal	CSE	Epidural	Lidocaine infusion	PCA	Simple analgesia	TAP block	Other
Right hemicolectomy	295 (61.6)	2 (0.4)	11 (2.3)	13 (2.7)	78 (16.3)	36 (7.5)	21 (4.4)	23 (4.8)
Left hemicolectomy (including sigmoidectomy)	321 (65.1)	2 (0.4)	19 (4)	14 (2.9)	65 (13.6)	28 (5.8)	16 (3.3)	23 (4.8)
Anterior resection	305 (63.7)	5 (1)	36 (7.5)	15 (3.1)	64 (13.4)	16 (3.3)	17 (3.5)	21 (4.4)
Abdomino-perineal resection (including ELAPE)	261 (54.5)	12 (2.5)	92 (19.2)	10 (2.1)	60 (12.5)	10 (2.1)	7 (1.5)	27 (5.6)
TaTME	249 (52)	6 (1.3)	33 (6.9)	8 (1.7)	51 (10.6)	58 (12.1)	4 (0.8)	70 (14.6)

Values are frequency (%).

CSE, combined spinal epidural; ELAPE, extralevator abdominoperineal excision; PCA, patient controlled analgesia; TAP, transversus abdominis plane; TaTME, transanal total mesorectal excision.

(range 200–1500)). The median of the maximum dose administered by anaesthetists was 600 µg (IQR 500–1000 (range 200–2000)) (figure 1).

A weak but statistically significant, positive correlation was found between the number of patients anaesthetised per month by each anaesthetist and the dose of intrathecal diamorphine used, both in terms of each anaesthetist's usual dose (spearman's $\rho=0.113$, $p=0.0337$) and maximum dose used (spearman's $\rho=0.105$, $p=0.047$).

Most anaesthetists performed the intrathecal injection prior to induction of general anaesthesia, regardless of whether surgery was predicted to take less than 2–3 hours, or more than 3–4 hours (77.8% and 74.1% respectively; table 2). A minority of anaesthetists performed intrathecal injection between induction of general anaesthesia and the surgical incision, or at the end of surgery prior to emergence from anaesthesia. Overall, estimated duration of surgery did not affect anaesthetists' timing of intrathecal injection delivery ($p=0.3297$, χ^2 test).

DISCUSSION

This large national clinician survey of analgesia for elective laparoscopic colorectal resections demonstrated that intrathecal analgesia is the most common primary mode of analgesia for these operations, with more than 80% of anaesthetists using it for postoperative pain. Epidural analgesia has been historically associated with effective postoperative pain control and improved pulmonary function after major abdominal surgery, but these advantages have not translated to faster recovery and shorter length of hospital stay.^{24 25} Moreover, technical difficulties while siting epidurals lead to failure rates of up to 40%²⁶ and the motor blockade caused by epidural analgesia delays patients' return to mobility. Spinal analgesia is technically less complex, requiring a single injection and no catheter placement. Patients who receive spinal analgesia report less postoperative pain than those who

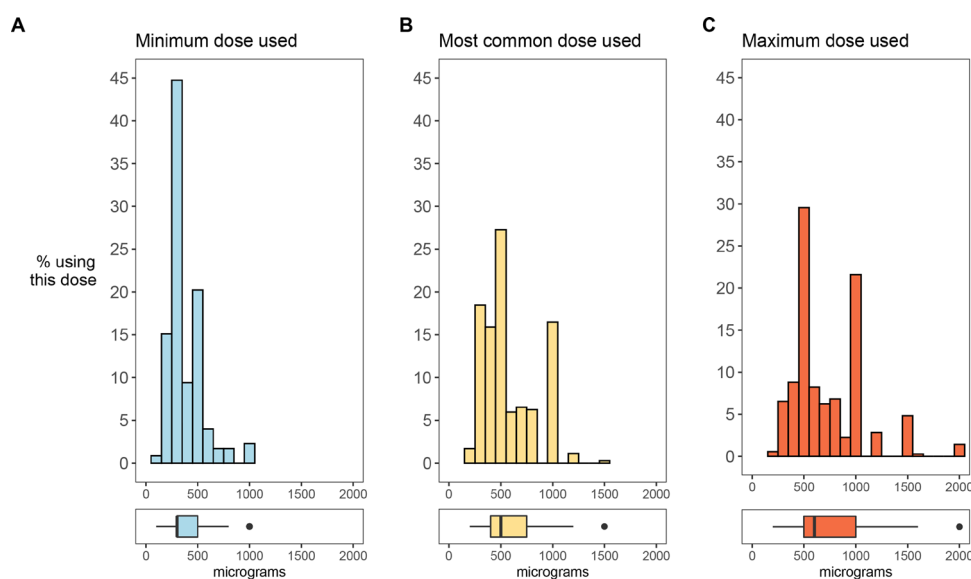


Figure 1 Doses of intrathecal diamorphine administered by anaesthetists. (A) minimum dose used, (B) most common dose used and (C) maximum dose used. Histograms demonstrate the percentage of anaesthetists who use each particular dose. The boxplots show overall range (horizontal black line), with IQR (central rectangle) and median (vertical black line). Outliers are depicted as dots.

**Table 2** Timings of spinal anaesthesia delivery dichotomised by predicted surgical duration

Predicted procedure length	Spinal anaesthesia prior to induction of anaesthesia	Spinal anaesthesia between induction of general anaesthesia and surgical incision)	Spinal anaesthesia after the end of surgery but prior to emergence from anaesthesia	Spinal anaesthesia not used routinely
<2–3 hours	372 (77.7)	19 (4)	13 (2.7)	75 (15.7)
>3–4 hours	355 (74.1)	20 (4.2)	23 (4.8)	81 (16.9)

Values are frequency (percentage).

receive TEA, require less intensive nursing care postoperatively and return to mobility faster.²⁷

Our survey showed that diamorphine is the most common drug (88%) used for intrathecal analgesia. Diamorphine's favourable pharmacokinetic and pharmacodynamic properties provide greater duration of action than fentanyl, with reduced cephalad spread (and subsequent risk of respiratory depression) than morphine. The longer duration of action with low side effect profile explains the widespread use of diamorphine for intrathecal use compared with other opioids for laparoscopic colorectal surgeries.

The median dose of diamorphine reported to be routinely used in our study was 500 µg, although with high interuser variability. Virlos *et al*²⁷ used doses between 1000 µg and 1500 µg for their study comparing intrathecal analgesia vs epidural analgesia for laparoscopic colorectal surgery.²⁷ In a major bariatric centre, doses of intrathecal diamorphine between 600 µg and 1500 µg were used for patients.²⁸ Similarly, our survey showed a large variability in respondents' usual administered diamorphine doses for major laparoscopic colorectal surgery (range 200–2000 µg), with most anaesthetists using 300, 500 or 1000 µg. We found a weak positive correlation between the number of patients anaesthetised for laparoscopic colorectal resections per month by each anaesthetist and the doses of intrathecal diamorphine they administer. This may indicate that anaesthetists with greater monthly caseloads (a surrogate for greater experience) believe the higher doses offer patients more effective analgesia, or have a different perspective on risks of higher doses. Despite substantial intrathecal diamorphine dosing variability between anaesthetists in our study, and also in previous reports, dose–response studies of ITD are presently limited to anaesthesia for obstetric and orthopaedic surgery and have not investigated the reasons for variation in dosing.^{29 30} The wide variation in ITD dosing suggest a lack of consensus on the optimal dose of ITD. This should be the topic of a future trial, and an embedded mixed-methods study could investigate the magnitude and drivers of the relationship between anaesthetists' caseload and higher administered ITD doses.

Our study has several limitations, chiefly related to the nature of questionnaire completion and the questions asked. We did not assess the impact of patients' demographic or clinical characteristics on ITD dosing, nor was there an option for respondents to elaborate on their responses via free text. As such, we cannot elaborate on the

factors influencing dose choices. The self-administered nature of survey and unknown overall response rate may lead to differences between reported and actual clinical practice. Furthermore, as we did not capture granular data regarding location of respondent, we cannot know if there is a variation in practice between larger and smaller hospitals, or if respondents are clustered within a certain region (limiting the study's validity as a measure of pan-UK practice). These points considered, the survey received 479 responses and so represents the largest such study of practice in this arena conducted to date. Despite this though, findings from this UK dataset may not be applicable to other health systems (most notably the USA, where diamorphine is not used).

High-quality prospective, randomised dose–response trials in the colorectal population are needed to investigate the relationship between doses of ITD and patient outcomes in this population. These studies should be designed to individualise ITD doses and ensure that outcome measures are both patient centred and clinically relevant.

CONCLUSION

Intrathecal opiate—usually diamorphine—is the form of postoperative analgesia most used by anaesthetists for patients undergoing major elective laparoscopic colorectal surgery in the UK. The median dose of diamorphine administered is 500 µg but with wide variation. Estimated duration of surgery did not influence postoperative analgesia choice or timing of spinal administration. Given wide variation in spinal diamorphine dosing, randomised dose-finding trials are needed in this cohort to determine optimal dosing.

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REFERENCES

- Gustafsson UO, Scott MJ, Hubner M, *et al.* Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS[®]) society recommendations: 2018. *World J Surg* 2019;43:659–95.
- Wu CL, Cohen SR, Richman JM, *et al.* Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. *Anesthesiology* 2005;103:1079–88.
- Tikuišis R, Miliauskas P, Samalavičius NE, *et al.* Intravenous lidocaine for post-operative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. *Tech Coloproctol* 2014;18:373–80.
- Fares KM, Mohamed SA-E, Abd El-Rahman AM, *et al.* Efficacy and safety of intraperitoneal dexmedetomidine with bupivacaine in laparoscopic colorectal cancer surgery, a randomized trial. *Pain Med* 2015;16:1186–94.
- Levy BF, Scott MJ, Fawcett W, *et al.* Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery. *Br J Surg* 2011;98:1068–78.
- Bonjer HJ, Deijen CL, Abis GA, *et al.* A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015;372:1324–32.
- Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. *Dis Colon Rectum* 2001;44:1083–9.
- Hübner M, Blanc C, Roulin D, *et al.* Randomized clinical trial on epidural versus patient-controlled analgesia for laparoscopic colorectal surgery within an enhanced recovery pathway. *Ann Surg* 2015;261:648–53.
- Cook TM, Counsell D, Wildsmith JAW, *et al.* Major complications of central neuraxial block: report on the third national audit project of the Royal College of anaesthetists. *Br J Anaesth* 2009;102:179–90.
- Hindle A. Intrathecal opioids in the management of acute postoperative pain. in: continuing education in anaesthesia. *Critical Care & Pain* 2008:81–5.
- Nair GS, Abrishami A, Lermite J, *et al.* Systematic review of spinal anaesthesia using bupivacaine for ambulatory knee arthroscopy. *Br J Anaesth* 2009;102:307–15.
- Meylan N, Elia N, Lysakowski C, *et al.* Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* 2009;102:156–67.
- Hudcova J, McNicol E, Quah C, *et al.* Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. *Cochrane Database Syst Rev* 2006:CD003348.
- Goettsch WG, Sukeel MPP, van der Peet DL, *et al.* In-hospital use of opioids increases rate of coded postoperative paralytic ileus. *Pharmacoepidemiol Drug Saf* 2007;16:668–74.
- Gabriel RA, Swisher MW, Sztain JF, *et al.* State of the art opioid-sparing strategies for post-operative pain in adult surgical patients. *Expert Opin Pharmacother* 2019;20:949–61.
- NHS E. A- Z list of all NHS acute (Hospital) trusts in England, 2016. Available: <https://www.nhs.uk/services/directories/pages/nhstrustlisting.aspx> [Accessed 09 Apr 2022].
- Wales N. NHS Wales | hospitals, 2006. Available: <http://www.wales.nhs.uk/ourservices/directory/hospitals> [Accessed 09 Apr 2022].
- Organisations – Scotland's Health on the Web. Available: <https://www.scot.nhs.uk/organisations/> [Accessed 09 Apr 2022].
- Trusts & Hospitals – Northern Ireland Medical & Dental Training Agency. Available: <https://www.nimtda.gov.uk/international-graduates-page/trusts-hospitals/> [Accessed 14 Apr 2022].
- Burns KEA, Duffett M, Kho ME, *et al.* A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ* 2008;179:245–52.
- R Core Team. R: a language and environment for statistical computing. Vienna, Austria R Foundation for Statistical Computing; 2020. <https://www.R-project.org/>
- Wickham H, Chang W, Henry L. ggplot2: create elegant data Visualisations using the grammar of graphics, 2021. Available: <https://CRAN.R-project.org/package=ggplot2> [Accessed 17 Jul 2021].
- Pedersen TL. *patchwork: The Composer of Plots*, 2020. Available: <https://CRAN.R-project.org/package=patchwork> [Accessed 17 Jul 2021].
- Turunen P, Carpelan-Holmström M, Kairaluoma P, *et al.* Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. *Surg Endosc* 2009;23:31–7.
- Khan SA, Khokhar HA, Nasr ARH, *et al.* Effect of epidural analgesia on bowel function in laparoscopic colorectal surgery: a systematic review and meta-analysis. *Surg Endosc* 2013;27:2581–91.
- Levy BF, Tilney HS, Dowson HMP, *et al.* A systematic review of postoperative analgesia following laparoscopic colorectal surgery. *Colorectal Dis* 2010;12:5–15.
- Virlos I, Clements D, Beynon J, *et al.* Short-term outcomes with intrathecal versus epidural analgesia in laparoscopic colorectal surgery. *Br J Surg* 2010;97:1401–6.
- Wojcikiewicz TG, Jeans J, Karmali A, *et al.* The use of high-dose intrathecal diamorphine in laparoscopic bariatric surgery: a single-centre retrospective cohort study. *Br J Pain* 2019;13:106–11.
- Stacey R, Jones R, Kar G, *et al.* High-dose intrathecal diamorphine for analgesia after caesarean section. *Anaesthesia* 2001;56:54–60.
- Jacobson L, Kokri MS, Pridie AK. Intrathecal diamorphine: a dose-response study. *Ann R Coll Surg Engl* 1989;71:289–92.