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Patient-Controlled Epidural Analgesia (PCEA) Versus Intravenous Patient-Controlled Analgesia (IV PCA) for Acute Postoperative Pain Relief in Minimally Invasive Abdominal Surgeries: A Systematic Review

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Abstract— To reduce acute postoperative pain in major abdominal surgeries, patient-controlled epidural analgesia (PCEA) has been considered the gold standard. However, in recent years, its safety is being questioned as despite its low incidence rate of serious complications, these complications are often very dangerous nevertheless. On the other hand, for minimally invasive surgeries (MIS) with estimated reduced postoperative pain, intravenous patient-controlled analgesia (IV PCA) is seen as a possibly more effective alternative due to the autonomy and satisfaction given to the patient. A systematic review of previous RCTs and clinical trials of patients undergoing abdominal MIS was done to compare acute postoperative pain, length of hospital stay, time to first flatus, and incidence of postoperative nausea and vomiting (PONV) between PCEA and IV PCA. During movement, pain scores consistently showed a lower pain score in the PCEA group rather than the IV PCA group, because epidural analgesia with local anesthetics blocks non-nociceptive stimuli on top of nociceptive stimuli.Only 1 study showed > 0.1 day difference in length of stay after surgery. The IV PCA group took a longer time to first flatus andshowed a higher percentage of patients experiencing PONV than in the PCEA group. This is correlated to administering systemic opioids, which are known to reduce propulsive contractions, prolong gut transit time, and largely stimulates the medulla's vomiting centre. This review showed that incidence of severe complications in PCEA proves to be low and is therefore the best method to reduce postoperative pain in abdominal MIS.

Keywords— Patient-controlled epidural analgesia, Intravenous patient-controlled analgesia, Acute postoperative pain, Minimally invasive abdominal surgery, Systematic Review

1. Introduction

Pain is a common and expected complaint among postoperative patients. Even though pain is common, it should not be disregarded. Inappropriate treatment of pain has been known to lead to increased infection rate, prolonged mechanical ventilation, prolonged opioid use, hemodynamic derangements, delirium, and compromised immunity [1-3]. In the long term, it leads to conditions such as persistent post-surgical pain, depression, post traumatic stress disorder, increased morbidity, and ventilation-associated pneumonia [4].

To reduce acute postoperative pain, multiple techniques of administration exist, from systemic to regional., from intramuscular to intravenous [5]. For the longest time, regional techniques, namely

epidural analgesia, have been considered the gold standard [6]. Level I evidence shows that it can reduce pulmonary, thromboembolic, and cardiovascular complications. Moreover, surgical stress response and requirements for other analgesics are also reduced [7]. However, despite its low incidence rate of serious complications, these complications are often very dangerous nevertheless. They include epidural hematoma (leading to neurological paralysis), epidural abscess, and postdural puncture headache [8].

It has a technical failure of 18.7% in the first 72 hours after administration, which mainly includes, Dolin, Cashman, and Bland (2002) list, premature catheter dislodgement, unsuccessful placement, unilateral block, and missed segments. [9] This is worrisome, taking into consideration the fact that this is the period of time when an average of 80.3% of patients undergoing elective surgery experience severe pain at some time [10].

In recent years, intravenous patient-controlled analgesia (IV PCA) is seen as a more effective alternative due to the autonomy given to the patient. IV PCA is an infusion pump that can be electronically controlled with the push of a button. Therefore, patients can administer analgesia themselves when they feel pain.Though it can be expensive, IV PCA is said to result in higher patient satisfaction and earlier hospital discharge [11].

Though epidural analgesia is the gold standard for major abdominal surgeries, what differentiates minimally invasive surgeries (MIS) from major abdominal surgeries is the reduced incision size which consequently allows reduced postoperative pain. As according to Davies et al (2013), given that epidural analgesia is associated with reduced mobilisation, increased IV fluid requirements, increased time to return of bowel function, and increased length of stay (LOS) in the hospital; IV PCA with morphine may be the better option for MIS [12,13].

However, more trials need to be studied to determine the reduction in pain scores in these two methods and their clinical importance as studies show conflicting results between these 2 methods [14]. Therefore, this study aims to summarise and measure the efficacy of patient-controlled epidural analgesia (PCEA) compared to intravenous patient-controlled analgesia (IV PCA) in patients undergoing abdominal surgery. In addition, this study will discuss their safety and impact on length of hospital stay (LOS).

PICO Formulation— In patients undergoing abdominal surgery, does intravenous patient-controlled analgesia, compared to patient-controlled epidural analgesia, decrease acute postoperative pain?

2. Material and Methods

2.1 Study Design

This study is a systematic review of previous randomized controlled trials and clinical trials of patients undergoing minimally invasive abdominal surgery anytime between 2000-2020. The approach used for data synthesis is a qualitative approach.

Definitions

Postoperative pain: Ceyhan and Güleç (2010) define postoperative pain as a condition of tissue injury together with muscle spasm after surgery [15]. They can be categorised to acute or chronic, with acute pain being pain up to 7 days after surgery [16].

Minimally invasive surgery (MIS): A minimally invasive surgery (MIS) is defined as one that "is safe and is associated with a lower postoperative patient morbidity compared with a conventional approach for the same operation" [17]. In abdominal surgeries, laparoscopy is a common type of minimally invasive surgery. Laparoscopy is often referred to as keyhole surgery and is a type of endoscopy. It is defined as "the inspection of the peritoneal cavity through the use of a small incision" [18].

2.2 Search Methods for Identification of Studies

The following databases were used by the authors:

- Cochrane Controlled Register of Trials (CENTRAL)
- Pubmed
- ScienceDirect
- ClinicalTrials.gov

The search strategy can be found in Appendix 1. No language restrictions were applied. The author did not contact other authors nor search for unpublished journals.

2.3 Inclusion Criteria

Types of Studies

- Randomized controlled trials (RCTs)
- Clinical trials

Types of Participants

- Adults of both genders
- Adults aged 18 or above
- Inpatients receiving abdominal surgery

Types of Interventions

- Intravenous PCA with opioids and/or local anesthetics

Comparison

- Thoracic or lumbar patient-controlled epidural analgesia

Types of Outcome Measures

- Primary outcome:
  - Visual Analog Scale (0 to 100)
- Secondary outcomes:
  - Length of hospital stay (days)
  - Time to first flatus (hours)
  - Incidence of postoperative nausea and vomiting (percentage)

2.4 Exclusion Criteria

- References published more than 20 years ago
- Evidence other than RCTs and controlled clinical trials
- Reviews and editorials
- Patients receiving emergency surgery
- Drugs administered in non-parenteral routes
- Patients also receiving non-pharmacological treatment
- Quadriplegic patients

- Contraindications to epidural catheter placement (e.g. infection in site of placement, coagulopathy)
- Allergy to systemic opioids or local anesthetics

There were no language restrictions nor geographic criteria for this study.

2.5 Data Collection and Analysis

Selection of Studies

Studies were selected by two authors. Titles and abstracts that clearly did not fit the inclusion criteria were immediately excluded. All remaining papers' full copies were obtained and read. Papers nor their authors were not blinded in any way before being presented to the authors. Any disagreements were resolved by a third author.

Data Extraction and Management

Data from all papers were entered into the Cochrane DPLP Data Collection Form for Intervention Reviews: RCTs and non-RCTs. They were then entered into Review Manager.

The data that were collected are as follows:

- Age of participants
- Gender of participants
- Number of participants enrolled in the study
- Location of study
- Type of surgery
- IV PCA drugs, bolus dose, lockout interval., background infusion
- Epidural analgesia drugs, bolus dose, lockout interval., and background infusion
- Pain intensity at any time it was assessed
- Length of hospital stay (readiness of discharge)
- Time to first flatus
- Incidence of postoperative nausea and vomiting

2.6 Assessment of Risk of Bias

The authors used the Cochrane Risk of Bias Tool to assess included studies in the following domains: sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential threats to validity.

3. Results

3.1 Search Results

Searches were run on July 2020. The authors searched through several databases including Pubmed, Cochrane CENTRal., ScienceDirect, and Scopus. Clinicaltrials.gov was also searched for additional information. The authors used various search strategies customized to each database, which can be found in Appendix 1. The first hit brought together a total of 476 studies. After removing the duplicates, the number of studies that remain is 450. These studies were screened by title and abstract, and a total of 438 were excluded. Then, the remaining full texts were scanned, in which 5 were excluded due to inappropriate study methods, and 1 study showing no results. With those being excluded, finally, 7 studies were deemed eligible for this review [19-25].

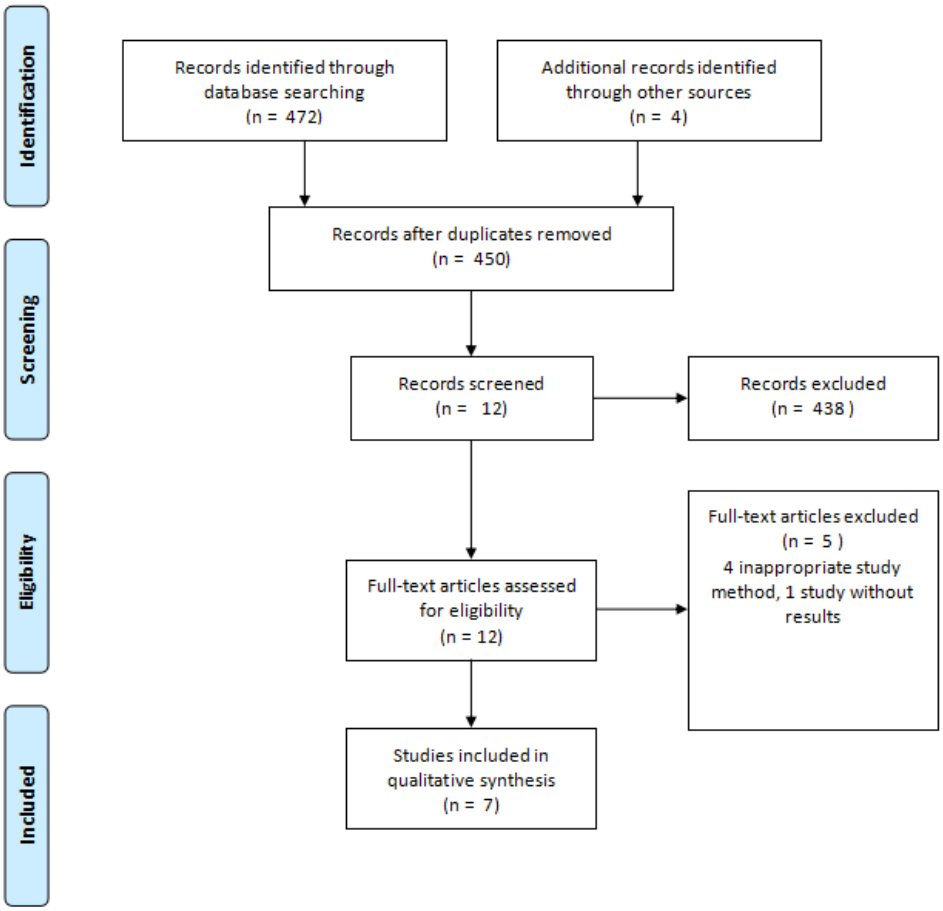

Fig 3.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram

3.2 Included Studies

Risk of Bias

Overall, the included studies have low risk of bias. The figure shows "some concerns" in 4 studies because when even 1 field has some concerns, the algorithm considers the overall study to have some concerns. However, these concerns are not major. The prevailing concern that is consistent throughout these studies is that the authors only mentioned that patients received information for consent about both interventions. The authors did not state whether or not the patients are aware of which intervention they are receiving. The authors did not explicitly state either whether outcome assessors were aware of the intervention the patient was receiving. With this in consideration, judgement of the outcome (level of pain) could have been affected by knowledge of the intervention. 1 study (Taqi 2006) has a high risk of bias because patients were not blinded and aware of the intervention, though they were not aware of the study hypothesis.

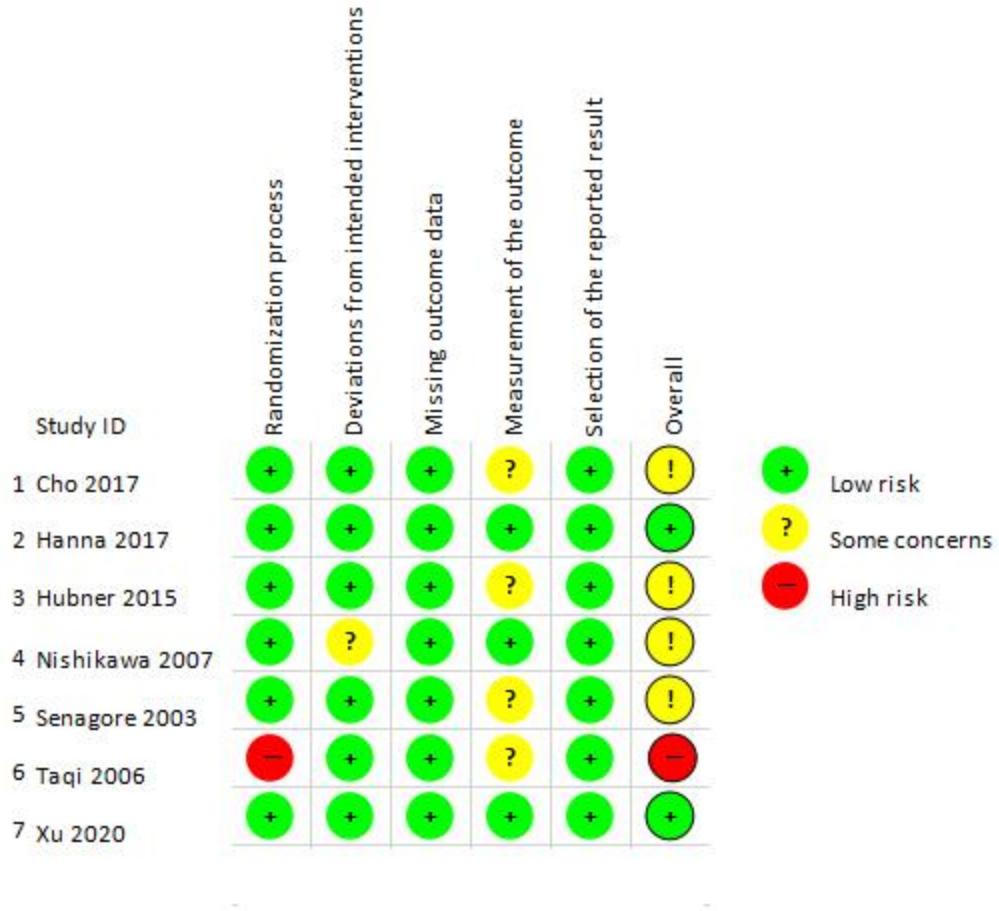

Fig 3.2 Risk of Bias of Included Studies

Participants

This systematic review collected studies with 686 patients enrolled, of which 192 were excluded due to not meeting the inclusion criteria, refusal to participate, and other unknown reasons. The final number of participants involved is 494. Most studies allowed for a wide age range (20-80 years old), except for Nishikawa 2007 which specifically targeted patients > 65 years old. However, even the lowest mean age in an included study was 51.7 years old (Cho 2017).

Almost all the included studies involved more men than women in the groups, except in Senagore 2003's PCEA group which had 9 men and 11 women. Body Mass Index (BMI) could not be displayed in the table of results due to a study (Senagore 2003) only reporting weight without height.

All studies utilise an ASA (American Society for Anesthesiologists) Physical Status Classification System to assess a patient's overall health pre-operation. More than 50% of all patients belong to ASA Grade II. 1 study (Cho 2017) did not classify all their patients. All studies did not include patients with an ASA Grade higher than IV except for 1 study (Hanna 2017) which had 4 ASA Grade IV patients.

Surgical Procedures

5 out of 7 studies focus on colorectal procedures such as colectomy, hemicolectomy, anterior resection,

and sigmoid resection. 1 study (Cho 2017) focuses on gastrectomies (subtotal., proximal., and total) while another (Nishikawa 2007) only performs cholecystectomies. All surgeries performed are confirmed to use

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No	Author	Methods	Participants	Other Drugs Administrated	IV PCA Group	EA Group	Outcomes Measured	Notes
1.	Cho et al., 2017	RCT	Patients (20–70 years old) with ASA Class I-III scheduled for laparos-copic gastric-tomy. N=86, 3 excluded (1 converted to open gastric-tomy, 2 received post-operative mechanical ventilation) Korean study.	Anesthesia: propofol 1.5–2.5 mg/kg and remifentanil 1μg/kg. Post-operative: ramosetron 0.3 mg IV to prevent PONV. Fentanyl 50 μg IV for acute pain relief. Rescue analgesic NRS >4: fentanyl 50μg. Additional: ketorolac. Rescue anti-emetic: metclo-pramide 10 mg IV	IV PCA group: Fentanyl 1.5 μg/kg. Total dose: 250 mL. Basal infusion: 5 mL/h. Bolus: 0.5 mL on demand. Lockout interval: 15 min.	Epi PCA group: 0.15% ropi-vacaine & fentanyl 2 μg/mL Total dose: 250 mL. Basal infusion: 5 mL/h. Bolus: 0.5 mL on demand. Lockout interval: 15 min. T8-9 or T9-10 inter-space	1. Time to first flatus 2. Time to first soft diet intake 3. Hemo-dynamic variables 4. Heart rate variability 5. Post-operative pain scores 6. Length of post-operative hospital stay 7. PCA compli-cations	

2.	Hanna et al., 2017	RCT, parallel group	Patients ≥ 18 years old undergoing elective lapa-roscopic large bowel resection or rectal resection with anas-tomosis. N=87, 8 excluded (4 did not meet inclusion criteria, 2 refusal to participate, 2 other reasons) American study.	Preoperative: alvimopan 12mg once Rescue analgesia: toradol IV, aceta-minophen PO or PR Postoperative: alvimopan PO until return of bowel function	IV PCA group: Hydro-mor-phone loading dose: 0.5mg. Bolus: 0.3 mg/10 mins. Maximal dose: 1.8 mg/h	Epi PCA group: Bupi-vacaine 0.1% & fentanyl 2µg/mL. Rate: 6-10 mL/h. Bolus: 3mL/40 mins. T10-T11 inter-space	1. Post-operative pain scores (VAS) 2. Side effects & quality of life 3. Readi-ness of hospital discharge

3.	Hubner et al., 2015	RCT, parallel group	Patients ≥ 18 years old undergoing elective laparos-copic colorectal surgery. N=266, 138 excluded (32 did not meet inclusion criteria, 90 declined to participate, 11 unable to consent, 5 unknown) Swiss study.	Anesthesia: propofol 1-2 mg/kg, fentanyl 2-3 µg/kg, cisatracurium 0.15-0.2 mg/kg via tracheal intubation. Maintained with sevoflurane. Baseline analgesic: paracetamol 4x1g/d & metamizole 4x500mg/d Rescue analgesia: morphine SC 0.1 mg/kg max 6x/d or buprenorphine SL 0.2-0.4 mg max 3x/d	IV PCA group: Demand dose: 1 mg/h. Bolus: 1 mL/ 5 mins. Maximal dose: 40 mg/4h	PCEA group: Bupi-vacaine 0.1%, fentanyl 2 µg/mL & adre-naline 2 µg/mL. Initial rate: 6-10 mL/h. Bolus: 3 mL/40 mins	1. Medical recovery (sufficient pain control, fully mobilized, tolerance of oral food) 2. Postoperative hospital stay 3. Length of stay in the high-depen-dency unit 4. Postoperative 30-day morbidity (major compli-cations) 5. Post-operative pain score (VAS) 6. Use of peri-operative vaso-pressor treatment up to POD 4	Use of ERAS guide-lines
4.	Nishikawa et al., 2007	RCT	Patients ≥ 65 years old, ASA status I-II, undergoing laparos-copic chole-cystectomy. N=30	Modified neurolept anesthesia (mNLA) for IV group: droperidol 0.2 mg/kg, pentazocine 0.3 mg/kg, thiamylal 2 mg/kg. Tracheal intubation. Mantained with	IV PCA group: bupre-norphine 20µg/mL & droperidol Bolus dose: 0.5	PCEA group: 0.125% bupi-vacaine, bupre-norphine µg/mL, and drope-ridol. Bolus: 2 mL. Lockout	1. Postoperative pain score at rest 2. Postoperative delirium 3. Patient satis-	

			Japanese study.	pentazocine. Anesthesia for Epi group: thiamylal 2 mg/kg. Tracheal intubation. Maintained with sevoflurane.	mL. Lockout interval: 15 min. Back-ground infusion: 0.5 mL/h.	interval: 60 min. Back-ground infusion: 2 mL/h. T7-T9 inter-space	faction
5.	Senagore et al., 2003	RCT	Patients undergoing segmental laparoscopic colectomy. N=47, 9 excluded (2 had no resection, 2 had second surgical procedure in same hospital stay, 5 had protocol violations). American study.	Anesthesia: propofol. Endotracheal intubation. Maintained by sevoflurane. Rescue analgesia: Morphine 1-4mg every 3-4h Post-operative: Diclofenac 50 mg oral., ketorolac 30 mg Antiemetic prophylaxis: dexame-thasone 8 mg, ondansetron 4 mg	IV PCA group: Infusion: bupi-vacaine 0.1% & fentanyl µg/mL. Rate: 4-6 mL/h.	PCEA group: 6-8mL bupi-vacaine 0.25% & fentanyl 1 mg before incision. Infusion: bupi-vacaine 0.1% & fentanyl µg/mL. Rate: 4-6 mL/h. T8-9 or T9-10 inter-space.	1. Post-operative pain score 2. Anal-gesic compli-cations

6.	Taqi et al., 2006	RCT	Consecutive patients undergoing elective laparoscopic colorectal surgery. N=50. Canadian study.	Anesthesia: propofol, fentanyl (100 µg for Epi group and 250 µg for IV group), rocuronium. Maintained with desflurane. Both groups: 500 mg naproxen 2x/day for 4 days. Aceta-minophen 1g 4x/day for 4 days.	IV PCA group: morphine. Rate: 1-2 mg/5 min. No back-ground infusion.	PCEA group: bupi-vacaine 0.1% & fentanyl 3 µg/mL. Rate: 5-15 mL/h. T8-T9 inter-space.	1. Time to flatus 2. Time to bowel movement 3. Postoperative pain score at rest, coughing, with ambu-lation 4. Fatigue VAS 5. PONV 6. Time out of bed 7. Time of hospital discharge (readiness for discharge and length of stay)
7.	Xu et al., 2020	RCT	Participants 20-80 years old undergoing laparoscopic colorectal cancer surgery. N=120, 30 excluded (20 did not meet inclusion crietria, 10 declined to participate).	Anesthesia: propofol 1-2 mg/kg, sufentanil 0.3 µg/kg. Maintained with ondansentron. Post-operative: flurbiprofen axetil 50 mg IV every 12h for 48h Rescue analgesia: sufentanil 5-10 µg	IV PCA group: sufentanil 0.2-0.4 µg/kg/h. bolus: 2 mL. Lockout interval: 15 min. Back-ground infusion: 2-5 mL/h	PCEA group: ropi-vacaine 0.15% & sufentanil 0.5 µg/mL. Bolus: 3 mL. Lockout interval: 15 min. Back-ground infusion: 4 mL/h. T9-T12 inter-space.	1. Length of hospital stay from surgery 2. Post-operative pain score 3. Time to return of bowel function 4. Time to mobile-zation

	Chinese study.	5. Urinary catheter removal 6. Sensory disturbance 7. Postoperative hyper-tention 8. Plasma levels of VEGF-C, IL-6, adrenaline, and cortisol

Table 3.1 Summary of Results

No.	Author	Group	Sample	Age	Sex (M/F)	ASA Class				Type of Surgery (n)
						I	II	III	IV	
1.	Cho et al., 2017	IV PCA	42	54.1 ± 10.5	24/18	-	17	4	-	Subtotal gastrectomy (34) Proximal subtotal gastrectomy (4) Total gastrectomy (4)
		PCEA	41	51.7 ± 10.7	23/18	-	16	3	-	Subtotal gastrectomy (33) Proximal subtotal gastrectomy (2) Total gastrectomy (6)
2.	Hanna et al., 2017	IV PCA	41	53 ± 14	26/15	0	29	8	4	Right colectomy/ileocecal resection (8) Left colectomy/sigmoid resection (11) LAR/protectomy (20) Total/subtotal colectomy (1) Abdominoperineal resection (1)
		PCEA	38	60 ± 12	20/18	0	11	27	0	Right colectomy/ileocecal resection (8) Left colectomy/sigmoid resection (11) LAR/protectomy (13) Total/subtotal colectomy (3) Abdominoperineal resection (3)
3.	Hubner et al., 2015	IV PCA	57	61.2 ± 17.8	24/23	7	41	9	0	Left/sigmoid colectomy (27) Right ileocecal resection (13) Rectum/(sub)total (11)
		PCEA	65	63.1 ± 15.1	37/28	6	49	10	0	Left/sigmoid colectomy (30) Right ileocecal resection (18) Rectum/(sub)total (10)
4.	Nishikawa et al., 2007	IV PCA	15	71.2 ± 5.3	8/7	3	12	0	0	Cholecystectomy
		PCEA	15	70.9 ± 6.5	9/6	4	11	0	0	Cholecystectomy
5.	Senagore et al., 2003	IV PCA	20	54 ± 13	12/8	1	14	5	0	Right colectomy/ileocolectomy (4) Sigmoid resection (10)
		PCEA	18	53 ± 16	9/11	0	12	6	0	Right colectomy/ileocolectomy (6) Sigmoid resection (12)
6.	Taqi et al., 2006	IV PCA	25	61.24 ± 14.91	13/12	2	15	8	0	Right hemicolectomy (11) Transverse colectomy (1) Left hemicolectomy (2) Sigmoid resection (8) Anterior resection (3) Total colectomy (0)

		PCEA	25	65 ± 16.18	14/11	3	17	5	0	Right hemicolectomy (12) Transverse colectomy (0) Left hemicolectomy (4) Sigmoid resection (3) Anterior resection (4) Total colectomy (2)
7.	Xu et al., 2020	IV PCA	60	58 4	37/23	8	44	8	0	Right hemicolectomy (21) Left hemicolectomy (8) Anterior resection (20) Sigmoid resection (11)
		PC EA	60	61 4	36/24	7	43	10	0	Right hemicolectomy (23) Left hemicolectomy (10) Anterior resection (16) Sigmoid resection (11)

Table 3.2 Sample Characteristics

laparoscopic methods. All studies only included elective (scheduled) surgeries and not emergency surgeries, except Xu 2020 which does not state whether or not emergency surgeries are included in the study.

Types of Anesthesia

All studies used general anesthesia and tracheal intubation for its administration. In all the studies, both treatment groups received the same anesthesia, except in Nishikawa 2007 where the IV PCA group received modified neurolept anesthesia (droperidol 0.2 mg/kg, pentazocine 0.3 mg/kg, thiamylal 2 mg/kg) and the PCEA group received thiamylal 2 mg/kg. Propofol is the most commonly used drug for anesthesia although with slightly differing doses. Other drugs used include fentanyl, alfentanil, remifentanil, and rocuronium. Anesthesia was maintained with sevoflurane in 5 studies. In Taqi 2006, it was maintained with desflurane while in Xu 2020, it was maintained with ondansentron.

Intravenous PCA Group

Drugs administered in the IV PCA group had more variation than in the PCEA group. Common drugs administered were bupivacaine and fentanyl. Morphine was also administered in Taqi 2006. Other drugs include hydromorphone (Hanna 2017), buprenorphine (Nishikawa 2007), droperidol (Nishikawa 2007), and sufentanil (Xu 2020). 4 studies (Cho 2017, Nishikawa 2007, Senagore 2003, Xu 2020) performed a background infusion in addition to the bolus. Cho 2017 and Xu 2020 set their lockout interval to 15 minutes, but Nishikawa 2007 set it to 60 minutes.

Epidural Analgesia Group

All 7 studies inserted the epidural catheter into the thoracic space and none into the lumbar space. 7 did not conduct continuous epidural infusion. The most common drugs administered were ropivacaine, fentanyl, bupivacaine. Other drugs include sufentanil (Xu 2020), buprenorphine (Nishikawa 2007), droperidol (Nishikawa 2007), and adrenaline (Hubner 2015).

Other Drugs Administered

Several studies mentioned the administration of certain drugs right after surgery to manage acute postoperative pain. All 8 studies provided, at the least, rescue analgesia, and also rescue antiemetics to adhere to hospital protocols. Rescue analgesics were for uncontrolled acute pain, which can be defined as persistent NRS > 4.

3.3 Excluded Studies

A large portion of studies in ScienceDirect, despite a specific search strategy, were immediately excluded due to their irrelevance. There were several most common reasons that caused a study to be excluded. The first is that irrelevant interventions (e.g. transverse abdominis plane block and paravertebral blocks) were performed on the patient instead of IV PCA and epidural analgesia. The second is the irrelevant participant in which the trial also included patients undergoing open surgery. 4 studies were excluded after reading the full texts. Gorevski et al., 2011 only stated “PCA users and nonusers” in their abstract, in which the full text revealed that nonusers did not include epidural analgesia. Kikuchi et al., 2018 showed no study results. Levy et al., 2011 administered continuous infusion instead of PCEA. Milan et al., 2011 included patients undergoing open surgery. Wongyingsinn et al., 2011 had an irrelevant study method, where IV lidocaine was the main intervention and PCA was only given when lidocaine was insufficient.

3.4 Effects of Interventions on Outcomes

Postoperative Pain Score

Pain score was measured by the Visual Analogue Scale (VAS) in all studies. This review differentiates the

No.	Author	Group	POD 0		POD 1		POD 2		POD 3	POD 4
			0h	12h	24h	36h	48h	60h	72h	96h
1.	Cho et al., 2017	PCA	5.1 ± 1.4		3.9 ± 1.6		4.3 ± 1.7			
		EA	4.4 ± 1.8		4.2 ± 1.7		4.6 ± 1.8			
3.	Hubner et al., 2015	PCA	2.7 ± 2.3		2.2 ± 2.0	2.4 ± 2.4	1.7 ± 1.8	1.8 ± 2.2	1.9 ± 2.2	0.9 ± 1.6
		EA	1.8 ± 2.4		1.7 ± 1.9	2.1 ± 2.6	1.5 ± 1.9	2.0 ± 2.3	1.2 ± 1.7	0.9 ± 1.6
5.	Nishikawa et al., 2007	PCA	0.5 ± 0.8	0.4 ± 0.7						
		EA	1.4 ± 1.5	0.8 ± 1.9						
7.	Taqi et al., 2006	PCA			4.0 ± 2.9		3 ± 2.8		3 ± 2.5	2 ± 2.6
		EA			1 ± 1.6		0 ± 1.4		1 ± 2.3	1 ± 1.8
8.	Xu et al., 2020	PCA	2.6 ± 0.9		2.1 ± 0.7		1.8 ± 0.7			
		EA	1.8 ± 0.5		1.6 ± 0.5		1.6 ± 0.5			

Table 3.3 Postoperative Pain Scores At Rest (VASr). Values are in mean ± standard deviation. POD: Post-operative day. PCA: patient-controlled analgesia. EA: epidural analgesia.

No.	Author	Group	POD 0		POD 1		POD 2		POD 3	POD 4
			0h	12h	24h	36h	48h	60h	72h	96h
6.	Senagore et al., 2003	PCA	6.6 ± 2.2		3.3 ± 0.8	2.1 ± 1.3				
		EA	2.2 ± 1.6		1.9 ± 1.7	1.7 ± 1.2				
7.	Taqi et al., 2006	PCA			7 ± 2.9		6 ± 3.3		3 ± 3.0	5 ± 3.1
		EA			3 ± 2.4		3 ± 2.3		4 ± 2.7	4 ± 2.3
8.	Xu et al., 2020	PCA	5.5 ± 1.5		5.1 ± 1.3		4.7 ± 1.1			
		EA	4.1 ± 1.1		4.0 ± 1.1		3.7 ± 1.1			

Table 3.4 Postoperative Pain Scores On Movement, Cough, Ambulation. Values are in mean ± standard deviation. POD: Post-operative day. PCA: patient-controlled analgesia. EA: epidural analgesia.

No.	Authors	PCA	EA
1.	Cho et al., 2017	6.0 ± 1.7	5.9 ± 1.9
2.	Hanna et al., 2017	4.0 ± 3.0	4.0 ± 3.0
3.	Senagore et al., 2003	2.3 ± 1.3	2.4 ± 0.8
4.	Taqi et al., 2006	5.0 ± 6.7	5.0 ± 1.9
5.	Xu et al., 2020	3.3 ± 0.7	4.1 ± 0.9

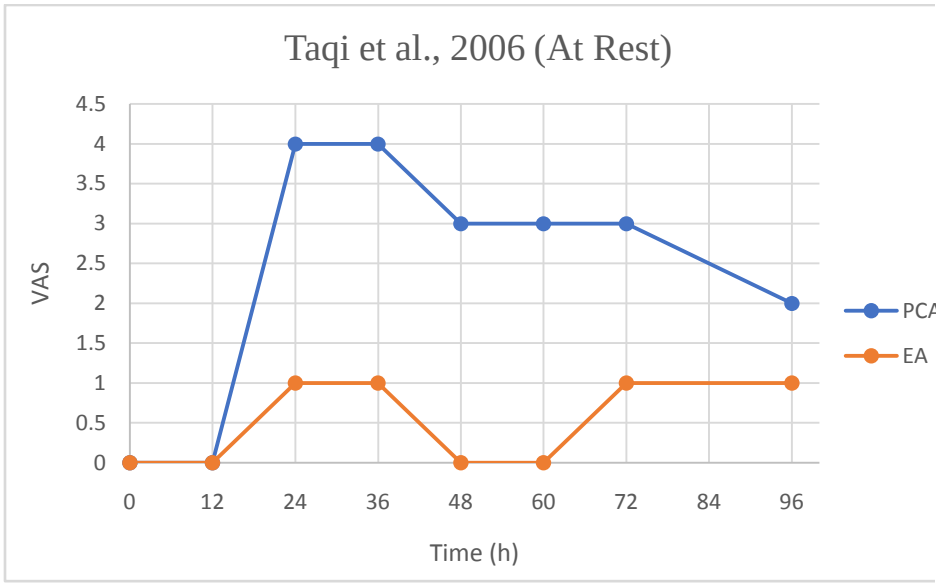
Table 3.5 Length of Stay After Surgery (d). Values are in mean ± standard deviation. PCA: patient-controlled analgesia. EA: epidural analgesia.

No.	Authors	PCA	EA
1.	Cho et al., 2017	70.0 ± 12.3	61.3 ± 11.1
2.	Hanna et al., 2017	48.0 ± 24.0	48.0 ± 24.0
3.	Taqi et al., 2006	72.0 ± 31.8	57.3 ± 29.3
4.	Xu et al., 2020	41.0 ± 15.1	34.0 ± 11.3

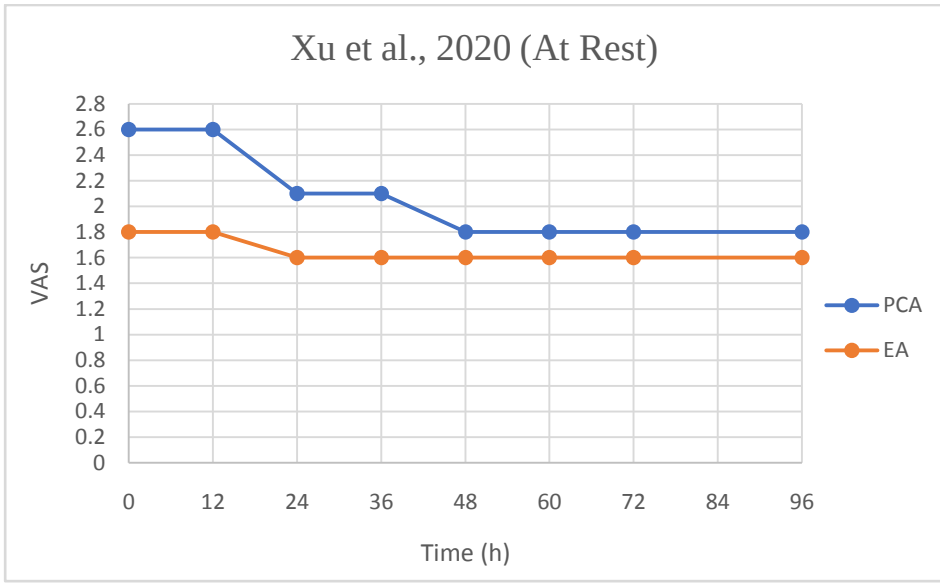
Table 3.6 Time to first flatus (h). Values are in mean ± standard deviation. PCA: patient-controlled analgesia. EA: epidural analgesia.

No.	Authors	PCA	EA
1.	Cho et al., 2017	19	14.6
2.	Hanna et al., 2017	36.5	31.5
3.	Nishikawa et al., 2007	20	13.3
4.	Senagore et al., 2003	30	33.3
5.	Xu et al., 2020	27	16

Table 3.7 Postoperative nausea and vomiting (%). PCA: patient-controlled analgesia. EA: epidural analgesia.

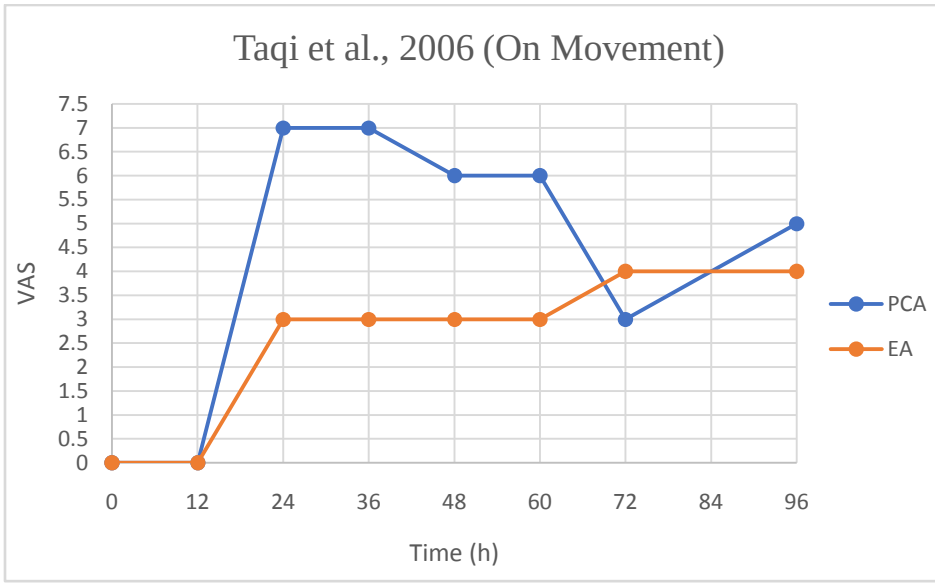


A



B

Fig 3.3 Postoperative Pain Scores at Rest, **A** Taqi 2006 **B** Xu 2020



A

B

Fig 3.4 Postoperative Pain Scores on Movement, Coughing, **A** Taqi 2006 **B** Xu 202

VAS measurements into 2 groups: VAS at rest (VASr) and VAS on movement, coughing, or mobilization (VASm). As each study measures the patients' VAS at different intervals, not every column of the table could be filled. At rest, the gap in pain scores between the two treatment groups is not very significant. In fact, there are varying results in which Hubner 2015, Taqi 2006, and Xu 2020 show higher VAS scores in the IV PCA group whereas Cho 2017 and Nishikawa 2007 show higher VAS scores in the PCEA group. On the other hand, the VASm scores consistently show a higher pain score in the IV PCA group rather than the PCEA group.

Length of Stay After Surgery

Studies sometimes differentiate between length of stay (LOS) and readiness for discharge. Readiness for discharge is a more sensitive unit of measure as length of stay can sometimes indicate that a patient is still hospitalised beyond medical readiness (BMR). However, studies that do not differentiate between these two mostly use length of stay as a unit of measure.

1 study (Hubner 2015) could not be included in this table as days were measured in median ± interquartile range instead of mean ± standard deviation. 1 study (Nishikawa 2007) did not measure the patients' LOS. 5 studies show < 0.1 day difference in LOS between the IV PCA and PCEA group. Only Xu 2020 showed significant difference, where the IV PCA group's mean LOS was 3.3 days whereas the PCEA group's was 4.1 days.

Time to First Flatus

Hanna 2017 showed that in both groups, the same duration was required until the first flatus. However, in all the other studies (Cho 2017, Taqi 2006, Xu 2020), the IV PCA group took a longer time to first flatus. The longest time it took was 72 hours (IV PCA group, Taqi 2006). The shortest time it took was 34 hours (PCEA group, Xu 2020). The largest difference between the IV PCA and PCEA group is 14.7 hours in Taqi 2006's study. Hubner 2015, Nishikawa 2007, and Senagore 2003 did not measure the time to first flatus.

Postoperative Nausea and Vomiting

Postoperative nausea and vomiting is a common side effect from opioids. In 4 out of 5 studies (Cho 2017, Hanna 2017, Nishikawa 2007, Xu 2020), the IV PCA group showed a higher percentage of patients experiencing PONV than in the PCEA group. The mean percentage of patients experiencing PONV in the IV PCA group is 26.5% whereas it is 21.7% for the PCEA group. Hubner 2015 did not measure PONV. Taqi 2006 also measured PONV, but differentiated between nausea and vomiting.

4. Discussion

4.1 Sample Characteristics

The lowest mean age in an included study was 51.7 years old. In 2005-2009, The National Cancer Database Report on CRC states that patients under 54 account for only 18.6% of all colorectal cancer patients [26]. Given that most of the studies included in this review performed colorectal procedures for benign and malignant colorectal diseases, this finding is consistent with the existing epidemiology that states that patients are mostly over 50 years old. It is also in line with other studies, which show a median age of 54 years old among 116 patients [27]. In addition, the study that did not focus on the colorectal area, i.e. that focused on cholecystectomy, specifically targeted patients > 65 years old.

15 out 16 treatment groups in the review involved more men than women. Seeing that 6 of the 8 studies were performed in the colorectal area, this finding is consistent with other studies that state that laparoscopic colorectal patients are more likely to be male [28]. The American Cancer Society (2020) also shows a

slightly higher number of estimated new colorectal cancer cases and estimated deaths in males than females [29].

4.2 Effects on Primary Outcome

Data could not be pooled at any time point for both VAS at rest and VAS on movement, coughing, and ambulation. However, through the table, it is observed that the difference in VAS scores between the two groups is more significant on movement than at rest. The minimum clinically important difference (MCID) is a measure of how much does a patient's pain score need to change for it to be considered meaningful. In this case, the MCID for VAS is 1 or 10 mm [30]. With reference to that, at rest, pain is mostly controlled in both groups. During movement, the PCEA group provided more pain relief than the IV PCA group.

There are several proposed mechanisms to explain why epidural analgesia is more effective than IV PCA. Epidural analgesia with local anesthetics does not only block nociceptive input, but also non-nociceptive stimuli. This mechanism is what helps reduce stimuli into the central nervous system that is responsible for pain. When combined with an opioid, the analgesic effect of the epidural will be even greater [31].

4.3 Effects on Secondary Outcomes

Length of Stay

Length of stay is an important indicator of a patient's recovery and a hospital's level of service. The longer the length of stay, the higher the chance of a patient succumbing to nosocomial infections. A more sensitive indicator would be the time to readiness for discharge because patients are occasionally still admitted in the hospital despite being ready for discharge or beyond medical readiness (BMR).

Length of stay greatly varies on an individual's pre-existing medical condition as well. For example, Hanna 2017, unlike the other studies, has decided to include patients of ASA Grade IV (patients with a severe systemic disease that is a constant threat to their life) into their trial as well, although these patients only constituted a small portion of her sample. It is expected for patients of ASA Grade IV to have a longer LOS than Grade II patients despite receiving the same treatment. Nonetheless, this does not seem to affect the final results much, as both treatment groups from Hanna 2017 showed the same LOS with the same standard deviation.

The longest LOS was found in Cho 2017's study i.e. 6 days. The shortest LOS is 2.3 days in Senagore 2003's study. 4 out of 5 studies show a difference of < 0.1 day in LOS between the 2 treatment groups. Considering that there is a difference in outcomes between the IV PCA and the PCEA group, the fact that the LOS between these two treatment groups is similar implies that the LOS does not vary due to the received treatment. Had it been due to the treatment they received, the LOS would have varied more. Rather, it may be more of a reflection of the healthcare service in that respective hospital.

Time to First Flatus

The results of the review show that the PCEA group took a shorter time to overcome postoperative ileus (POI). Postoperative ileus is caused by, among others, surgical trauma, with complicated mechanisms: autonomic nervous system, neurotransmitters, local factors, hormones, and inflammation [32].

Epidural analgesia is known to reduce postoperative ileus through a sympathectomy. A sympathectomy is the blocking of a nerve in the sympathetic trunk. When a sympathectomy occurs, the parasympathetic

nervous system activity, which is responsible for increased gut motility, is preserved. In addition to that, the vagus nerve is where the parasympathetic system innervates the gut up to the splenic flexure. It is located cranially to the effect of the thoracic epidural analgesia, thus the parasympathetic efferent nerves are unopposed by the analgesic.

A way to further increase this effect is to administer local anesthetics instead of systemic opioids. Systemic opioids are known to reduce propulsive contractions and prolong gut transit time [33]. The PCEA group mostly used bupivacaine and ropivacaine, a local anesthetic. In comparison, the IV PCA group, besides bupivacaine, mainly used systemic opioids such as fentanyl and morphine. This may be the reason why the IV PCA group took longer to the first flatus.

Nonetheless, to restore bowel function, 3 out of 4 studies administered drugs in the postoperative phase which are known to be able to reduce postoperative ileus. Xu 2020 chose flurbiprofen axetil, a potent NSAID which is known to reduce POI [34]. NSAIDs restore bowel function by inhibiting COX-2, which at normal conditions, does not affect bowel function, but in intraoperative settings, encourages small intestine contractility [35]. Taqi 2006 also chose to administer an NSAID i.e. naproxen.

Hanna 2017 chose alvimopan per oral until bowel function is restored. Alvimopan is a peripherally acting mu-opioid antagonist. In postoperative settings, opioids are continuously used for postoperative pain relief. Tolerance towards its pain-relieving effects may develop, but tolerance towards opioids' gastrointestinal adverse effects does not. Therefore, an opioid antagonist is useful to counteract opioids and decrease POI significantly [36]. Cho 2017 did not administer drugs to prevent POI, which might have been the reason their patients had the longest mean time to first flatus.

Incidence of Postoperative Nausea and Vomiting

4 out of 5 studies show that a higher percentage of patients in the IV PCA group experienced postoperative nausea and vomiting compared to the PCEA group. This finding is consistent with previous studies that show that opioids are known to induce central nervous system adverse effects such as nausea and vomiting in up to 40% of patients [37,38].

Postoperative opioid treatment is an established risk factor of PONV [39]. The effect is largely dose-dependent. Opioids such as fentanyl and morphine induce nausea by activating the D2 receptors in the chemoreceptor trigger zone (CTZ), which in turn stimulates the vomiting center in the medulla, which activates the vomiting reflex [40].

The highest mean incidence of PONV occurred in Hanna 2017's study. The patients in this study were not given anti-emetic drugs, or none that the authors of this review know of. Patients were only given alvimopan until return of bowel function, which is a drug with nausea as one of its adverse effects [41]. The lowest mean incidence of PONV was in Cho 2017's study. Patients in Cho 2017's study were given ramosetron 0.3 mg intravenously to prevent PONV.

The only study that shows a higher percentage of PONV in the PCEA group is Senagore 2006. This may have been due to the fact that they are the only study who used the exact same drugs in both treatment groups (bupivacaine and fentanyl). In addition to that, the PCEA group received extra bupivacaine and fentanyl before incision, which may have contributed to the PONV.

Conclusion and Recommendation

Patient-controlled epidural analgesia is superior to intravenous patient-controlled analgesia in the following outcomes: postoperative pain score on movement, cough, and ambulation; time to first flatus; and postoperative nausea and vomiting.Patient-controlled epidural analgesia and intravenous patient-controlled analgesia are somewhat equal to each other in terms of length of stay.PCEA was doubted due to safety reasons. However, incidence of severe complications is low.Therefore, the author concludes that the best method to reduce postoperative pain is patient-controlled epidural analgesia (PCEA).

There are several limitations to this systematic review. Due to the limited search results, there was large heterogeneity in the data available. This rendered the author unable to generate a quantitative synthesis, and so the effect size of each outcome could not be measured.

Competing Interests

The authors declarethat there is no conflict of interest.

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Appendix 1

Search Strategy

Cochrane CENTRAL

#1	MeSH descriptor: [Analgesia, Epidural] explode all trees	1998
#2	((PCEA OR CEA OR TEA OR thoracic epidural OR lumbar epidural)):ti,ab,kw	7884
#3	#1 OR #2	9179
#4	MeSH descriptor: [Analgesia, Patient-Controlled] explode all trees	2026
#5	((intravenous patient-controlled analgesia OR iv patient-controlled analgesia OR iv pca OR pca OR pcia OR intravenous pca)):ti,ab,kw	6667
#6	#4 OR #5	7206
#7	MeSH descriptor: [Laparoscopy] explode all trees	5639
#8	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees	27600
#9	#7 OR #8	27600
#10	#3 AND #6 AND #9	30

Pubmed

analgesia AND (epidural OR TEA OR PCEA OR CEA) AND (patient-controlled OR PCA OR PCIA) AND (laparoscop*)

Filter: Clinical Trials, RCT

ScienceDirect

(epidural analgesia OR "thoracic epidural") AND (intravenous "patient-controlled analgesia" OR PCIA OR PCA) AND (laparoscopic)

Filters: Review Articles

ClinicalTrials.gov

epidural AND (patient-controlled OR PCA OR PCIA)

Filter: Study Type: Interventional., Study Results: With Results

Appendix 2
List of Abbreviations

- BMR : Beyond medical readiness
- EA : Epidural analgesia
- IV PCA : Intravenous patient-controlled analgesia
- LOS : Length of stay
- MCID : Minimum clinically important difference
- MIS : Minimally invasive surgery
- PCEA : Patient-controlled epidural analgesia
- POD : Post-operative day
- POI : Post-operative ileus
- PONV : Post-operative nausea & vomiting
- VAS : Visual Analogue Scale