What is the impact of dexamethasone on postoperative pain in adults undergoing general anaesthesia for elective abdominal surgery: a systematic review and meta-analysis

Ciara Mitchell (cmitchell11@qub.ac.uk)
UCL: University College London https://orcid.org/0000-0003-2981-2099
C. Mitchell
UCL: University College London
S. J. Cheuk
Royal Group of Hospitals and Dental Hospital Health and Social Services Trust: Belfast Health and Social Care Trust
C. M. O'Donnell
Royal Group of Hospitals and Dental Hospital Health and Social Services Trust: Belfast Health and Social Care Trust
S. Bampoe
UCL: University College London
D. Walker
UCL: University College London

Research

Keywords: dexamethasone, postoperative pain, abdominal surgery

Posted Date: May 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-558680/v1

Abstract

Background

Previous meta-analysis of heterogeneous surgical cohorts demonstrated reduction in postoperative pain with perioperative intravenous dexamethasone, but none have addressed adults undergoing elective abdominal surgery.

Objective

To determine the impact of intravenous perioperative dexamethasone on postoperative pain in adults undergoing elective abdominal surgery under general anaesthesia.

Methods

This review was prospectively registered on the international prospective register of systematic reviews (CRD42020176202). Electronic databases Medical Analysis and Retrieval System Online (MEDLINE), Exerpta Medica Database (EMBASE), (CINAHL) Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and trial registries were searched to January 28 2021 for randomised controlled trials, comparing dexamethasone to placebo or alternative antiemetic, that reported pain. The primary outcome was pain score, and secondary outcomes were time to first analgesia, opioid requirements and time to post-anaesthesia care unit (PACU) discharge.

Results

Fifty-two studies (5768 participants) were included in the meta-analysis. Pain scores ≤4 hours were reduced in patients who received dexamethasone at rest (mean difference (MD), -0.54, 95% confidence interval (CI) -0.72 to -0.35, I^2 = 81%) and on movement (MD -0.42, 95% CI -0.62 to -0.22, I^2 = 35). In the dexamethasone group 4–24 hour pain scores were less at rest (MD -0.31, 95% CI -0.47 to -0.14, I^2 = 96) and on movement (MD -0.26, 95% CI -0.39 to -0.13, I^2 = 29) and pain scores ≥24 hours were reduced at rest (MD -0.38, 95% CI -0.52 to -0.24, I^2 = 88) and on movement (MD -0.38, 95% CI -0.65 to -0.11, I^2 = 71). Time to first analgesia (minutes) was increased (MD 22.92, 95% CI 11.09 to 34.75, I^2 = 98), opioid requirements (mg oral morphine) decreased (MD -6.66, 95% CI -9.38 to -3.93, I^2 = 88) and no difference in time to PACU discharge (MD -3.82, 95% CI -10.87 to 3.23, I^2 = 59%).

Conclusions

Patients receiving dexamethasone had reduced pain scores, postoperative opioid requirements and longer time to first analgesia. Dexamethasone is an effective analgesic adjunct for patients undergoing abdominal surgery.

Background

Pain is a common postoperative problem and can be associated with physical and psychological sequelae. Glucocorticoids can modify the stress response and reduce inflammation. Dexamethasone, a commonly used antiemetic, interferes with the cyclooxygenase and lipoxygenase pathways through phospholipase inhibition and has been proposed to modulate postoperative pain in surgical patients [1].

Two reviews, Waldron et al. and De Oliveira et al., established a reduction in postoperative pain from a single perioperative dose of dexamethasone in heterogeneous surgical cohorts with debated clinical significance [1–3]. Additionally, they demonstrated dexamethasone's opioid sparing effects but produced conflicting conclusions regarding the dose-response relationship [2,3]. Therefore, the analgesic benefit of glucocorticoids in abdominal surgery remains unclear [4,5]. Waldron et al. excluded patients who received intrathecal or epidural local anaesthetics or opioids yet regional anaesthesia plays a key role in opioid-sparing analgesia for major abdominal surgery [3]. Furthermore, patients who received multiple doses of dexamethasone were excluded potentially limiting their clinical significance considering the surgical stress response extends beyond the period of surgery.

Given the exclusion criteria in reviews to date, it is unclear if any benefit demonstrated from the use of dexamethasone in heterogenous cohorts can be translated into patients undergoing elective abdominal surgery.

Therefore, the aim of this review is to determine the effect of perioperative dexamethasone on postoperative pain in adults undergoing general anaesthesia for elective abdominal surgery.

Methods

This study was performed according to a prospectively registered protocol (CRD42020176202) and followed guidance from the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [6–8].

Randomised controlled trials (RCT) of adults, aged 18 or over, who received intravenous perioperative dexamethasone undergoing general anaesthesia alone or in combination with regional anaesthesia with pain as a primary or secondary outcome for elective abdominal surgery were included. Gastrointestinal, gynaecological and urological procedures were included but renal or transplant surgery were excluded. As the intention was to assess the impact of dexamethasone on postoperative pain, minor gynaecological procedures that were not considered to be painful for example diagnostic laparoscopy were excluded [9]. Studies were included if intravenous dexamethasone was given at any time, in any dose, either alone or in combination with other antiemetics with placebo or any combination of antiemetic drugs as the comparator. Other study drugs could be given provided the analgesic effect of dexamethasone could be isolated. The primary outcome of our review was pain scores reported on an 11-point numerical scale (0–10). Secondary outcomes for this study included time to first analgesia, opioid requirements and time to PACU discharge.

Literature Search

Electronic databases MEDLINE, EMBASE, CINAHL, CENTRAL and Web of Science were searched, with no language or date restrictions, for RCTs published up to January 28 2021. When available, a standardised search strategy to identify RCTs was used [10] and the full search strategy was published [8] (see Additional file 1). Grey literature and trial registers were searched as pre-specified however, due to the COVID-19 pandemic the World Health Organisation (WHO) International Clinical Trials Registry Portal (ICTRP) was temporarily closed to external users and not searched as pre-specified [11]. The reference lists of identified studies and relevant systematic reviews were scanned for additional evidence.

Two authors, (CM and SJC), independently screened unblinded citations, assessed full texts for eligibility, extracted data, recorded on a predetermined data extraction form (see Additional file 2) and assessed bias at outcome level using Cochrane guidance [12]. When necessary, a third author (CO'D) mediated any disagreements.

When the specific surgical procedure was not stated and attempts to contact the author failed, we excluded minor painless surgical procedures based on the length of surgery, anaesthetic and surgical technique, length of hospital stay and postoperative analgesic requirements. Pain scores were defined as early (≤4 hours), intermediate (4–24 hours) and late (≥24 hours) and pain scores presented as a range of times were allocated to the group they most closely corresponded, for example, zero to six hours was allocated to the early group. When multiple pain scores were presented for a single time interval the latest pain score was extracted. Pain scores were assumed to be at rest when this was not stated and converted from a 0-100 to a 0–10 scale as required. Opioids were combined to achieve the total postoperative dose and converted to oral morphine equivalents (see Supplementary Table 1, Additional File 3). Time to first analgesia and PACU discharge were collected in minutes. Authors were successfully contacted for unpublished data or study clarification in seven studies [13–19]. Data was extracted as mean and standard deviation or converted using verified methods [20–23]. Studies containing multiple groups were combined into those with dexamethasone, irrespective of dose or timing, and those not containing dexamethasone. When the analgesic effect of dexamethasone could not be isolated a subset of study data was included to exclude confounding analgesia.

Meta-analysis of outcome data using a random-effects model was performed using *Review Manager* (*(RevMan*) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020) and presented as MD with 95% CIs. Statistical heterogeneity was assessed using the method proposed by Higgins et al. (I^2 test) [24].

Results

Database and trial registry searches revealed a total of 2160 citations. 1846 irrelevant citations were removed, followed by 184 research and publication duplicates leaving 130 articles for eligibility assessment. Twelve articles by Fujii et al. and Schietroma et al. were excluded due to concerns over research validity and multiple retractions [25–28]. We were unable to obtain two full text articles and 13 non-English articles were removed. 103 articles remained for full text eligibility assessment. Studies failed to meet the inclusion criteria and were excluded for the following reasons; 23 articles reported no pain outcomes, three studies were not RCTs, two studies had mixed surgical cohorts, participants did not receive general anaesthesia in three studies, there was no intravenous comparator in four studies and in one the analgesic effect of dexamethasone could not be isolated. Seven studies with minor surgery were excluded [29–35]. A further 12 studies were excluded; two used an alternative method of pain assessment and 10 presented inadequate data for analysis that we were unable to obtain through contacting the

authors. 48 full text articles remained, and four additional studies were included after reference list searching resulting in 52 studies with a total of 5758 participants articles (Fig. 1).

Figure 1 PRISMA flow diagram detailing process of study selection.

The final included studies are summarised in the characteristics of included studies table (Table 1). All 52 studies were RCTs of adult patients undergoing general anaesthesia for abdominal surgery published in English. The most common dose of dexamethasone used was 8mg but ranged from 1.25-20mg. Four studies presented the dose of dexamethasone in $mg.kg^{-1}$ and were transformed into total doses using the mean study weights or the average weight of an adult at the time and location of the study [36–40]. No studies administered multiple doses of dexamethasone, but six studies included two or more different doses of dexamethasone [36,41–45]. A further two studies compared the same dose of dexamethasone at different times of administration [46,47]. Opioid doses presented in $mg.kg^{-1}$ were converted in a similar manner to dexamethasone [16,42,48].

Table 1
Included studies characteristics, intervention and control groups extracted, primary study outcome and pain outcomes reported.

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Alghanem 2010[68]	Jordan	Laparoscopic cholecystectomy	180	ASA ≤2 Age 18–70 Mix M/F	I: Intraoperative dexamethasone 8mg IV C: Ondansetron or saline	PONV	Pain scores
Areeruk 2016[49]	Thailand	Gynaecological laparotomy via pfannenstiel incision	49	ASA ≤2 Age 18–65	I: Intraoperative dexamethasone 8mg IV C: Saline	Total morphine consumption	Pain scores Opioid consumption
Badawy 2015[83]	Egypt	Total abdominal hysterectomy	38	ASA ≤2 Age 40–70	I: Preoperative dexamethasone 8mg IV + gabapentin 800mg PO C: Saline + gabapentin	Time to first analgesia	Pain scores Time to first analgesia Opioid consumption
Bataille 2016[13]	France	Laparoscopic sleeve gastrectomy	117	ASA ≤3 Age 18–75 BMI > 40 ≥2 RFs PONV Mix M/F	I: Intraoperative dexamethasone 4mg + ondansetron 4mg IV C: Saline	PONV	Pain scores
Batistaki 2019[67]	Greece	Laparoscopic cholecystectomy	44	ASA ≤3 Age 18–75 Predominantly female	I: Intraoperative dexamethasone 5mg C: Saline	Reversal NMB	Pain scores
Benevides 2013[71]	Brazil	Laparoscopic sleeve gastrectomy	60	ASA 1–3 Age 18+ BMI ≥35	I: Intraoperative dexamethasone 8mg + ondansetron 8mg IV C: Saline + ondansetron	PONV Rescue antiemetic use	Opioid consumption PACU LOS
Bianchin 2007[50]	Italy	Laparoscopic cholecystectomy	73	ASA ≤2 Predominantly female	I: Preoperative dexamethasone 8mg IV C: Saline	PONV	Pain scores
Biligin 2010[69]	Turkey	Total abdominal hysterectomy + bilateral salpingoophorectomy	160	ASA ≤2 Age 20–60	I: Preoperative dexamethasone 8mg IV C: Saline or ondansetron or metoclopramide	PONV	Pain scores

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Bisgaard 2003[51]	Denmark	Laparoscopic cholecystectomy	80	ASA ≤2 Age < 75 Predominantly female	I: Preoperative dexamethasone 8mg IV C: Saline	Pain Fatigue	Pain Scores Opioid consumption PACU LOS
Coloma 2002[52]	USA	Laparoscopic cholecystectomy	140	ASA ≤2 Predominantly female	I: Intraoperative dexamethasone 4mg IV C: Saline	Recovery times	Time to first analgesia Opioid consumption PACU LOS
Corcoran 2017[53]	Australia	Major laparoscopic gynaecological surgery	31	ASA ≤2 Age 18–60 Surgery > 90mins ≥1-night stay	I: Intraoperative dexamethasone 4mg IV C: Saline	Immune response	Pain scores
De Oliveira 2011[36]	USA	Laparoscopic gyanecological surgery	106	ASA ≤2	I: Preoperative dexamethasone 0.05 or $0.1mg.kg^{-1}$ IV C: Saline	QoR-40	Pain scores Time to first analgesia Opioid consumption
Elhakim 2002[41]	Egypt	Laparoscopic cholecystectomy	180	Predominantly male	I: Preoperative dexamethasone 2 or 4 or 8 or 16mg IV C: Saline or ondansetron	PONV	Pain scores Time to first analgesia Opioid consumption
Feo 2006[54]	Italy	Laparoscopic cholecystectomy	101	ASA ≤3 F > M	I: Preoperative dexamethasone 8mg IV C: Saline	Pain PONV Analgesic and antiemetic requirements	Pain scores
Fukami 2009[55]	Japan	Laparoscopic cholecystectomy	80	Mix M/F	I: Preoperative dexamethasone 8mg IV C: Saline	PONV Pain Fatigue Analgesic and antiemetic requirements	Pain scores
Gautam 2008[72]	Nepal	Laparoscopic cholecystectomy	142	ASA ≤2 Age 23–65	I: Preoperative dexamethasone 8mg IV or dexamethasone 8mg IV + ondansetron 4mg C: Ondansetron	PONV	Pain scores Time to first analgesia Opioid consumption

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Hammas 2002[82]	Sweden	Cholecystectomy, Inguinal hernia repair	76	ASA ≤2 Predominantly male	I: Intraoperative dexamethasone 4mg + ondansetron 4mg + droperidol 1.25mg + metoclopramide 10mg IV C: Propofol infusion	PONV	Opioid consumption
Ionescu 2014[56]	Romania	Laparoscopic cholecystectomy	42	ASA ≤2 Predominantly female	I: Preoperative dexamethasone 4mg IV C: Saline	Immune response	Opioid consumption
Jo 2012[14]	Korea	Laparoscopic cholecystectomy	120	ASA ≤2 Female Age 21–64 BMI < 35	I: Preoperative dexamethasone 8mg IV + saline intraoperative or preoperative dexamethasone 8mg IV + ramosetron 0.3mg IV intraoperative C: Saline + ramosetron	PONV	Pain scores
Jokela 2009[42]	Finland	Laparoscopic hysterectomy +/- oophorectomy	120	ASA ≤3 BMI < 35	I: Preoperative dexamethasone 5 or 10 or 15mg IV C: Saline	Pain Opioid consumption	Pain scores Time to first analgesia Opioid consumption
Kasagi 2013[73]	Japan	Hysterectomy, cystectomy, myomectomy	60	ASA ≤2 Age 20–50 Benign disease	I: Preoperative dexamethasone 8mg IV C: Droperidol	PONV	Pain scores
Kassim 2018[37]	Egypt	Laparoscopic gyanecological surgery for infertility	50	ASA ≤2 Age 25–35	I: Preoperative dexamethasone 0.1mg.kg^{-1} IV + duloxetine 60mg PO C: Saline + duloxetine	Pethidine requirements	Pain scores Time to first analgesia Opioid consumption
Ko-iam 2015[16]	Thailand	Laparoscopic cholecystectomy	100	ASA ≤2 Age 18–75 Predominantly female	I: Intraoperative dexamethasone 8mg + metoclopramide 10mg IV C: Metoclopramide	PONV	Pain scores Opioid consumption

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Kurz 2015[84]	USA	Colorectal resection	555	Age ≤80 Surgery 2–6 hours	I: Intraoperative dexamethasone 4mg IV & 30% oxygen or intraoperative dexamethasone 4mg IV & 80% oxygen C: Saline + oxygen	Surgical site infection	Pain scores
Lee 2017[40]	Republic of Korea	Laparoscopic cholecystectomy	380	ASA ≤2 Age 18–45 Mix M/F	I: Preoperative dexamethasone 5mg IV C: Saline	Morphine requirements	Pain scores Time to first analgesia Opioid consumption
Lim 2011[46]	Korea	Laparoscopic cholecystectomy	120	ASA ≤2 M > F	I: Preoperative dexamethasone 8mg + intraoperative saline or preoperative saline + intraoperative dexamethasone 8mg IV C: Saline	Pain	Pain scores Opioid consumption
Liu 1998[57]	Taiwan	Major gynaecological surgery	60	ASA ≤2	I: Intraoperative dexamethasone 10mg C: Saline	PONV Pain	Pain scores Opioid consumption
Liu 1999[43]	Taiwan	Abdominal and radical hysterectomy, myomectomy	150	ASA ≤2	I: Preoperative dexamethasone 1.25 or 2.5 or 5 or 10mg IV C: Saline	PONV	Pain scores Time to first analgesia Opioid consumption
Lopez-Olaondo 1996[74]	Spain	Major abdominal gynaecological surgery	100	ASA ≤2 Age 18–65 45-90kg	I: Preoperative dexamethasone 8mg + ondansetron 4mg IV C: Saline + ondansetron	PONV	Pain scores Opioid consumption
Maddali 2003[75]	Oman	Laparoscopic gyanecological surgery	120	ASA ≤2 Age ≤60	I: Preoperative dexamethasone 8mg + ondansetron 4mg IV or dexamethasone 8mg + metoclopramide 10mg C: Saline	PONV	Pain scores

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Mathiesen 2009[85]	Denmark	Abdominal hysterectomy +/- salpingoophorectomy	76	ASA ≤2 Age 18–75 BMI 18–32	I: Preoperative dexamethasone 8mg IV + paracetamol 1g PO + pregabalin 300mg PO C: Saline + paracetamol + gabapentin	Morphine consumption	Pain scores Opioid consumption
McKenzie 1997[80]	USA	Abdominal or vaginal hysterectomy, laparotomy, anterior and posterior repair	80	ASA ≤3 Age 18–65	I: Intraoperative dexamethasone 20mg IV + ondansetron 4mg IV C: Saline + ondansetron	PONV	Pain scores Opioid consumption
Murphy 2011[58]	USA	Laparoscopic cholecystectomy	115	ASA ≤3 F > M	I: Preoperative dexamethasone 8mg IV C: Saline	QoR-40	Pain scores Opioid consumption PACU LOS
Murphy 2014[44]	USA	Laparoscopic or open hysterectomy	195	ASA ≤3 Age 18–80	I: Intraoperative dexamethasone 4 or 8mg IV C: Saline	Perioperative glucose concentration	Pain scores Opioid consumption PACU LOS
Nesek-Adam 2007[76]	Croatia	Laparoscopic cholecystectomy	160	ASA ≤2 Predominantly female	I: Intraoperative dexamethasone 8mg IV + saline or dexamethasone 8mg + metoclopramide 10mg C: Saline or saline + metoclopramide	PONV	Pain scores Time to first analgesia
Olajumoke 2013[59]	Nigeria	Total abdominal hysterectomy, myomectomy	96	ASA ≤2 Age 18–65	I: Intraoperative dexamethasone 4mg IV C: Saline	PONV	PACU LOS
Pan 2008[77]	USA	Laparoscopic gynecological surgery	60	ASA ≤2 Age ≥18 ≥3 emetic risk factors	I: Intraoperative dexamethasone 8mg + ondansetron 4mg IV + ondansetron PO D0,1,2 C: Saline + ondansetron	PONV	Pain scores Opioid consumption PACU LOS

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Pauls 2015[60]	USA	Major vaginal reconstructive surgery	63	ASA ≤3	I: Preoperative dexamethasone 8mg IV C: Saline	Quality of recovery	Pain scores Opioid consumption
Regasa 2020[81]	Ethiopia	Major gynaecological surgery	96	ASA ≤2 Age 18–65	I: Intraoperative dexamethasone 8mg IV + saline or dexamethasone 8mg + metoclopramide 10mg C: metoclopramide	PONV	Opioid consumption
Rothenberg 1998[38]	USA	Laparoscopic gynaecological surgery	95	ASA ≤2	I: Intraoperative dexamethasone 0.17mg.kg^{-1} IV C: Droperidol	PONV	Pain scores Opioid consumption PACU LOS
Ryu 2013[78]	Korea	Laparoscopic cholecystectomy	72	ASA ≤2 Age 25–65	I: Intraoperative dexamethasone 8mg + ramosetron 0.3mg IV C: Saline + ramosetron	PONV	Pain scores
Sanchez-Ledesma 2002[15]	Spain	Hysterectomy, myomectomy/ adnexectomy, oncological gynaecological reduction	90	ASA ≤2 Age 18–65 45-90kg	I: Intraoperative dexamethasone 8mg + droperidol 1.25mg IV + postoperative droperidol or dexamethasone 8mg + ondansetron 4mg and postoperative saline C: Ondansetron + droperidol	PONV	Pain scores Opioid consumption
Sanchez-Rodriquez 2010[61]	Mexico	Laparoscopic cholecystectomy	210	ASA ≤2 Age ≤80 F > M	I: Preoperative dexamethasone 8mg IV C: Placebo	PONV Pain Fatigue Additional analgesic & antiemetic drugs	Pain scores
Shrestha 2014[79]	Nepal	Laparoscopic cholecystectomy	120	ASA ≤2 Age 17–75 Predominantly female	I: Preoperative dexamethasone 8mg + pheniramine 45.5mg IV C: Saline	Pain Systemic acute phase response	Pain scores

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Study 1st author year	Country	Procedures	Participants Included, no	Participant characteristics	Intervention(s) and Control(s)	Primary outcome(s)	Pain outcome(s) reported
Sistla 2009[62]	India	Laparoscopic cholecystectomy	70	Predominantly female	I: Preoperative dexamethasone 8mg IV C: Saline	Morphine consumption	Pain scores Opioid consumption
Thangaswamy 2010[45]	India	Total laparoscopic hysterectomy	55	ASA ≤2 Age 18–60	I: Preoperative dexamethasone 4 or 8mg IV C: Saline	Fentanyl consumption	Pain scores Time to first analgesia Opioid consumption
Tolver 2012[63]	Denmark	Transabdominal preperitoneal groin repair	73	ASA ≤2 Age 18–85	I: Preoperative dexamethasone 8mg IV C: Saline	Pain	Pain scores Opioid consumption
Viriyaroj 2015[64]	Thailand	Laparoscopic cholecystectomy	80	Predominantly female	I: Preoperative dexamethasone 8mg IV C: Saline	Pain Analgesic consumption	Pain scores Opioid consumption
Wang 1999[65]	Taiwan	Laparoscopic cholecystectomy	78	ASA ≤2 Age 30–55 Predominantly female	I: Preoperative dexamethasone 8mg IV C: Saline	PONV	Pain scores Opioid consumption
Wang 2000[47]	Taiwan	Total abdominal hysterectomy	120	ASA ≤2 Age 35–45	I: Preoperative dexamethasone 10mg IV + postoperative saline or preoperative saline + postoperative dexamethasone 10mg IV C: Saline	PONV	Pain scores Opioid consumption
Wu 2009[66]	Taiwan	Anorectal surgery	60	ASA ≤2 Predominantly female	I: Preoperative dexamethasone 5mg IV C: Saline	PONV	Pain scores Opioid consumption
Yuksek 2003[70]	Turkey	Laparoscopic gyanecological surgery	60	ASA ≤2 19–62	I: Preoperative dexamethasone 8mg IV C: Saline or ondansetron	PONV	Pain scores Time to first analgesia

PONV postoperative nausea and vomiting, NMB neuromuscular blockade, PACU LOS post-anaesthesia care unit length of stay

Dexamethasone was directly compared to placebo in 27 studies [36,40,42–47,49–67] with a further four comparing dexamethasone to placebo or another antiemetic [41,68–70]. Intravenous anti-emetic drugs were included in the intervention or control groups in 17 studies [13–16, 38,71–82]. One study compared dexamethasone with an intraoperative and postoperative propofol infusion [82]. Four studies included additional study drugs, but groups were extracted to ensure the analgesic effect of dexamethasone was isolated [37,83–85].

The timing of dexamethasone varied from two hours preoperatively to immediately after extubation [37,45,47]. Dexamethasone was most frequently given preoperatively [14,36,37,40–43,45–47,50,51,54–56,58,60–66,69,70,72–75,79,81,83,85], but when administered intraoperatively this was more

commonly postinduction pre-incision [13,15,38,44,49,52,53,57,59,67,68,71,76–78,80,82,84] than during the surgical procedure [16,46]. In one study dexamethasone was given immediately post extubation [47].

The primary outcome was most commonly related to PONV in 26 studies [13–16,38,41,43,47,50,59,65,66,68–78,80–82]. Pain outcomes were the primary outcome in 11 studies [37,40,42,45,46,49,62–64,83,85] and was a joint primary outcome in a further six studies [51,54,55,57,61,79]. The primary outcome was quality or timing of recovery in four studies [36,52,58,60], the immune or stress response in two studies [53,56], surgical site infection in one study[84], perioperative glucose concentration in one study [44] and reversal of neuromuscular blockade in one study[67]. In general, study outcomes were poorly documented with 25 studies not specifically stating study outcome [14,16,38,41–43,46,47,50,52,53,56,57,59,62,65,68–70,72,76,78,79,81,82], seven studies documenting primary outcome only [15,36,51,66,75,77,83] and ambiguity over primary or secondary outcomes in a further five studies [54,55,61,64,73].

Pain was presented on an 11-point numerical scale in the majority of studies and divided by 10 when presented as 0-100 [14,40,44,45,58,63,78,85]. Six studies did not report pain scores [52,56,59,71,81,82] and we were unable to extract pain scores in a further four studies [37,51,57,74]. The pain outcomes extracted from each study are presented in Table 2.

Table 2
Pain outcomes extracted from each study

	Pain Scores								
Study Year	Early Rest	Early Movement	Intermediate Rest	Intermediate Movement	Late Rest	Late Movement	Time to First Analgesia	Opioid Consumption	PACU LOS
Alghanem 2010[68]	yes				yes				
Areeruk 2016[49]			yes	yes	yes	yes		yes	
Badawy 2015[83]	yes		yes		yes		yes	yes	
Bataille 2016[13]	yes	yes			yes	yes			
Batistaki 2019[67]	yes		yes		yes				
Benevides 2013[71]								yes	yes
Bianchin 2007[50]	yes		yes		yes				
Bilgin 2010[69]			yes						
Bisgaard 2003[51]								yes	yes
Coloma 2002[52]							yes	yes	yes
Corcoran 2017[53]	yes	yes							
De Oliveira 2011[36]	yes						yes	yes	
Elhakim 2002[41]					yes	yes	yes	yes	
Feo 2006[54]	yes		yes		yes				
Fukami 2009[55]	yes		yes		yes				
Gautam 2008[72]	yes		yes		yes		yes	yes	
Hammas 2002[82]								yes	
Ionescu 2014[56]								yes	
Jo 2012[14]	yes		yes						
Jokela 2009[42]	yes	yes	yes	yes	yes	yes	yes	yes	
Kasagi 2013[73]	yes		yes						
Kassim 2018[37]							yes	yes	
Ko-iam 2015[16]			yes					yes	
Kurz 2015[84]	yes		yes						
Lee 2017[40]		yes		yes		yes	yes	yes	
Lim 2011[46]	yes		yes		yes			yes	
Liu 1998[57]								yes	
Liu 1999[43]					yes		yes	yes	
Lopez-Olaondo 1996[74]								yes	

PACU LOS, post-anaesthesia care unit length of stay

	Pain Scores								
Maddali 2003[75]			yes						
Mathiesen 2009[85]	yes	yes			yes	yes		yes	
McKenzie 1997[80]	yes				yes			yes	
Murphy 2011[58]	yes	yes	yes	yes				yes	yes
Murphy 2014[44]	yes	yes						yes	yes
Nesek-Adam 2007[76]	yes	yes	yes	yes			yes		
Olajumoke 2013[59]									yes
Pan 2008[77]	yes		yes		yes			yes	yes
Pauls 2015[60]					yes			yes	
Regasa 2020[81]								yes	
Rothenberg 1998[38]			yes					yes	yes
Ryu 2013[78]	yes		yes		yes				
Sanchez-Ledesma 2002[15]	yes		yes	yes	yes	yes		yes	
Sanchez-Rodriquez 2010[61]	yes		yes		yes				
Shrestha 2014[79]					yes				
Sistla 2009[62]	yes	yes	yes	yes	yes	yes		yes	
Thangaswamy 2010[45]	yes	yes	yes	yes	yes	yes	yes	yes	
Tolver 2012[63]			yes	yes	yes	yes		yes	
Viriyaroj 2008[64]	yes		yes		yes			yes	
Wang 1999[65]	yes							yes	
Wang 2000[47]	yes							yes	
Wu 2009[66]	yes								
Yuksek 2003[70]			yes				yes		

PACU LOS, post-anaesthesia care unit length of stay

Bias assessment judged seven studies to be low risk [15,37,45,58,63,72,80], 20 studies to have some concerns, [13,14,38,40,44,46,52,54,55,59,61,64,68,71,73,74,76,77,79,83] and 25 to be high risk [16,36,41–43,47,49–51,53,56,57,60,62,65–67,69,70,75,78,81,82,84,85]. For ROB assessment see Supplementary Table 2, Additional File 4 and Supplementary Figs. 1 and 2, Additional File 5.

Pain scores

Early pain scores at rest were recorded in 30 studies (3408 patients) [13–15,36,42,44–47,50,53–55,58,61,62,64–68,72,73,76–78,80,83–85] with a statistically significant reduction in pain in patients receiving dexamethasone (MD -0.54; CI -0.72, -0.35; I^2 81%; n = 3408) (Fig. 2). The direction of result remained unchanged when the analysis was restricted to studies with pain (MD -0.8; CI -1.22, -0.38; I^2 91%; n = 950) and non-pain (MD -0.4; CI -0.62, -0.19; I^2 63%; n = 2458) primary outcomes.

Figure 2 Forest plot for early (≤4 hours) VAS pain scores at rest.

Ten studies (1319 patients) reported early pain scores on movement [13,40,42,44,45,53,58,62,76,85] with a statistically significant reduction in pain in patients who received dexamethasone (MD -0.42; CI -0.62, -0.22; I^2 35%; n = 1319). The result trend did not vary when the analysis was limited to studies with non-pain (MD -0.47; CI -0.84, -0.10; I^2 52%; n = 618) or pain (MD -0.43; CI -0.68, -0.18; I^2 17%; n = 701) as the primary outcome.

Intermediate pain scores at rest were recorded in 27 studies (3022 patients) [14–16, 38,42,45,46,49,50,54,55,58, 61–64,67,69,70,72,73, 75–78,83,84] and on movement in nine studies (1112 patients) [15,40,42,45,49,58,62,63,76]. There was a statistically significant reduction in intermediate pain scores both at rest (MD -0.31; CI -0.47, -0.14; I^2 96%; n = 3022) and on movement (MD -0.26; CI -0.39, -0.13; I^2 29%; n = 1112) in patients receiving dexamethasone. When analysis of intermediate pain scores at rest was restricted to studies with pain as the primary outcome the direction of result remained (MD -0.57; CI -0.92, -0.22; I^2 89%; n = 996), however, lost statistical significance when restricted to non-pain primary outcomes (MD -0.18; CI -0.39, 0.03; I^2 97%; n = 2026). Restricting the results for intermediate pain scores on movement to pain (MD -0.33; CI -0.45, -0.21; I^2 0%; n = 747) and non-pain (MD -0.16; CI -0.25, -0.07; I^2 0%; n = 365) primary outcomes did not change the direction of the result.

Late pain scores at rest were recorded in 25 studies (2443 patients) [13,15, 41–43,45,46,49,50,54,55, 60–64,67,68,72, 77–80,83,85]. There was a statistically significant reduction in pain scores in patients who received dexamethasone (MD -0.38; CI -0.52, -0.24; I^2 88%; n = 2443). The direction of the result was unchanged when the study outcome was restricted to pain (MD -0.42; CI -0.68, -0.16; I^2 90%; n = 1192) and non-pain (MD -0.34; CI -0.57, -0.11; I^2 77%; n = 1251) primary outcomes.

Ten studies (1210 patients) [13,15, 40–42,45,49,62,63,85] reported late pain on movement with a statistically significant reduction in pain scores in patients who received dexamethasone (MD -0.38; CI -0.65, -0.11; I^2 71%; n = 1210). Confining the results to non-pain primary outcomes did not change the result trend (MD -0.49; CI -0.95, -0.03; I^2 59%; n = 387) but limiting to studies with pain as the primary outcome demonstrated no statistical significance (MD -0.3; CI -0.61, 0.00; I^2 66%; n = 823).

Analgesic requirements

Time to first analgesia was recorded in 12 studies (1581 patients) [36,37, 40–43,45,52,70,72,76,83]. There was a statistically significant increase in time to first analgesia (minutes) in patients who received dexamethasone (MD 22.92.; CI 11.09, 34.75; I^2 99%; n = 1581) (Fig. 3). Restricting the analysis to studies with pain (MD 31.97; CI 13.35, 50.60; I^2 99%; n = 643) and non-pain primary outcomes (MD 15.17; CI 0.33, 30.02; I^2 91%; n = 938) did not affect the trend.

Figure 3 Forest plot for time to first analgesia in minutes.

Postoperative opioids were recorded in 33 studies (3339 patients) [15,16,36–38,40–47,49,51,52,56–58,60,62–65,71,72,74,77,80–83,85]. However, there was variability in the type, administration and time of recorded opioids varying from one hour to five days postoperatively. There was a statistically significant reduction in opioid use (mg of oral morphine equivalents) in patients who received dexamethasone (MD -6.66; CI -9.38, -3.93; I^2 88%; n = 3339) (Fig. 4). Statistical significance remained when the result was restricted to pain (MD -8.35; CI -11.64, -5.07; I^2 58%; n = 1251) and non-pain (MD -5.50; CI -9.15, -1.85; I^2 91%; n = 2088) primary outcomes. Visual inspection of the funnel plots for total opioid requirements and early pain scores at rest do not suggest evidence of significant reporting or publication bias (see Supplementary Fig. 3 and Fig. 4, Additional File 6).

Figure 4 Forest plot for total postoperative opioid use in mg of oral morphine equivalents.

Time to PACU discharge

Nine studies (947 patients) reported time to discharge from PACU [36,38,44,51,52,58,59,71,77]. There was no difference in time to PACU discharge between patients who received dexamethasone and those who did not (MD -3.82; CI -10.87, 3.23; I^2 59%; n = 947). Removing the single study with pain as the primary outcome and restricting the analysis to non-pain (MD -4.37; CI -12.10, 3.37; I^2 54%; n = 867) had no impact on the result.

Subgroup analyses

Subgroup analyses of general anaesthesia in combination with either central neuraxial blockade (GA + CNB) or regional anaesthesia (GA + RA) were previously documented (CRD42020176202) [8]. Patients received GA + CNB in three studies; spinal with intrathecal morphine [15], epidural administration of morphine and fentanyl [70] and a small proportion of both the intervention and control groups received an epidural in one study [84]. The subset of study data was not available in this study.[84] One study documented the use of regional anaesthesia with either transversus abdominal plane block or rectus sheath block[81]. Given the limited data these predefined subgroup analyses were not undertaken.

The planned dosing subgroup analyses were undertaken for a single but not multiple doses of dexamethasone. Doses were grouped pragmatically into three categories to correspond with clinical practice; low dose 1.25-5mg, intermediate dose 6.4-10mg and high dose 11-

20mg. For early pain scores at rest both low (MD -0.55; CI -1.04, -0.07; I^2 66%; n = 1023) and intermediate (MD -0.55; CI -0.76, -0.34; I^2 83%; n = 2265) demonstrated benefit with no impact from high dose (MD -0.21; CI -1.02, 0.60; I^2 0%; n = 120). For early pain scores on movement only intermediate dose (MD -0.48; CI -0.75, -0.21; I^2 47; n = 587) demonstrated benefit with no impact from low (MD -0.34; CI -0.67, 0.00; I^2 0%; n = 692) or high dose (MD -0.40; CI -1.79, 0.99; n = 40).

For 4–24 hour pain scores, again, there was evidence of dose response for intermediate dose at rest (MD -0.36; CI -0.53, -0.18; I^2 96%; n = 2221) and on movement (MD -0.25; CI -0.37, -0.13; I^2 22%, n = 1005). There was a lack of statistical significance for low (MD 0.22; CI -0.15, 0.58; I^2 0%, n = 666) and high dose (MD -0.05; CI -0.76, 0.66; I^2 0%; n = 135) at rest and low (MD -0.12; CI -0.77, 0.54; I^2 0%; n = 67) and high dose (MD -0.70; CI -2.62, 1.22; n = 40) on movement.

Intermediate dose remained statistically significant (MD -0.42; CI -0.62, -0.22; I^2 84%; n = 1847) for late pain scores at rest but low (MD -0.08; CI -0.22, 0.06; I^2 19%; n = 431) and high (MD -0.51; CI -1.32, 0.30; I^2 66%; n = 165) dose dexamethasone demonstrated no difference (Fig. 5). This pattern was mirrored in late pain scores on movement; low (MD -0.25; CI -0.5, 0.00; I^2 0%; n = 274), intermediate (MD -0.47; CI -0.83, -0.10; I^2 70%; n = 851) and high dose (MD -0.31; CI -1.43, 0.82; I^2 74%; n = 85).

Figure 5 Forest plot for dexamethasone dosing late (≥24 hours) VAS pain scores at rest.

Time to first analgesia was increased with intermediate dose (MD 27.76; CI 13.96, 41.55; I^2 98%; n = 1034) but low (MD 11.58; CI -0.34, 23.5; I^2 89%; n = 462) and high dose had no impact (MD 25.44; CI -2.23, 53.12; I^2 86%; n = 85). Again, a statistically significant reduction in postoperative opioid requirements was maintained for intermediate dose (MD -7.20; CI -9.77, -4.64; I^2 80%; n = 2402) but low (MD -8.14; CI -16.72, 0.44; I^2 89%; n = 677) and high dose dexamethasone (MD -19.26; CI -57.79, 19.28; I^2 94%; n = 260) demonstrated no difference.

Subgroup analysis did not impact time to PACU discharge with no difference from low (MD 0.27; CI -6.72, 7.27; I^2 40%; n = 385), intermediate (MD -9.56; CI -24.56, 5.44; I^2 65%; n = 467) or high (MD -3.76; CI -15.77, 8.25; n = 95) dose dexamethasone (see supporting information, Appendix 3).

Timing of administration subgroup analyses of dexamethasone were also performed. This was categorised as preoperative (before anaesthetic induction), intraoperative (anaesthetic induction and to extubation) and postoperative (after extubation). The timing subgroup analyses demonstrated a global reduction in pain scores from preoperative administration of dexamethasone for all pain scores both at rest and on movement. In contrast, intraoperative administration only reduced late pain scores at rest.

Preoperative dexamethasone significantly increased time to first analgesia (MD 28.13; CI 14.57, 41.68; I^2 98%; n = 1281), but there was no difference from intraoperative administration (MD -0.01; CI -6.24, 6.21; I^2 0%; n = 300). Additionally, preoperative dexamethasone decreased total opioid administration (MD -8.55; CI -12.34, -4.76; I^2 89%; n = 2214) with no effect from intraoperative administration (MD -2.18; CI -5.93, 1.56; I^2 83%; n = 1065). Postoperative dexamethasone (MD -12.00; CI -17.45, -6.55; n = 40) decreased opioid administration but this was based on results from a single study.[47] Time to PACU discharge remained unaffected by dexamethasone timing; preoperative (MD -12.55; CI -30.73, 5.63; I^2 62%; n = 361), intraoperative (MD -0.56; CI -7.41, 6.29; I^2 57%; n = 586) (For additional forest plots see Additional File 7).

Discussion

To our knowledge this is the largest systematic review and meta-analysis investigating the effect of perioperative dexamethasone on postoperative pain in adults undergoing elective abdominal surgery under general anaesthesia and the first to demonstrate an important analgesic effect in this surgical cohort.

Our analyses demonstrated a statistically significant reduction in early, intermediate and late pain scores both at rest and on movement. Sub-group analyses revealed that intermediate dose (6.4-10mg) effectively decreased pain at all time intervals both at rest and on movement. However, low dose (1.25-5mg) only affected early pain scores at rest while high dose (11-20mg) had no impact on any pain scores. Preoperative administration of dexamethasone demonstrated a global reduction on all pain scores. Intraoperative administration was more beneficial in reducing late pain scores at rest but failed to impact pain at any other time period. Dexamethasone also reduced the total postoperative opioid requirements and increased the time to first analgesia with intermediate dose (6.4-10mg) and preoperative administration demonstrating the greatest impact. Time to PACU discharge was not altered by dexamethasone at any dose or time and is likely to be influenced by external factors [86]. However, this is contrary to previous findings which have questionable clinical significance [3].

Dexamethasone's established anti-inflammatory properties has ensured it is a widely used effective perioperative anti-emetic [1,5,87]. In abdominal surgery glucocorticoids reduce pro-inflammatory mediators and phospholipase required for pain pathways allowing its analgesic benefits to be increasingly recognized [1–3, 5]. Enhanced recovery pathways encouraging earlier mobility have boosted the demand for opioid-sparing

multimodal analgesia in patients undergoing abdominal surgery [88–91]. Dexamethasone has, therefore, an important role in postoperative analgesia with additional benefit for multimodal analgesic regimes in this patient population. However, full analgesic effect is unlikely from the commonly used lower anti-emetic dose and intermediate dose (6.4-10mg) is necessary to produce global reductions in pain scores, increase time to first analgesia and reduce opioid requirements [1,87]. Additionally, timing of administration is crucial as the analgesic benefits of preoperative dexamethasone far outweigh administration at induction as recommended for antiemetic effect [92].

One of the major strengths of this review is inclusion of a large number of studies and participants of a relatively homogenous surgical population. This allows the results to inform future clinical practice and guidelines in moderate and major abdominal surgery. A previous systematic review failed to demonstrate a reduction in early pain scores on movement from dexamethasone administration, likely due to small numbers [3]. This new finding is potentially significant for enhanced recovery regimes where early movement after abdominal surgery is encouraged [88–91]. In addition, investigation of dexamethasone's effect on intermediate pain scores is novel and provides further evidence of its analgesic effects [2,3]. Through subgroup analyses we have provided clarification on the debated perioperative dosing and given strength to the previously suggested preoperative timing [2,3]. Despite demonstrating a globally statistically significant reduction in postoperative pain scores it is important to remember that the clinical significance of this is uncertain. The increase in time to first analgesia and reduction in postoperative opioids is likely to have more clinical impact on patients undergoing abdominal surgery. When studies with regional anaesthesia were removed a statistically significant reduction in postoperative opioids (MD -6.87; CI -9.70, -4.05; I^2 89%; n = 3153) and increased time to first analgesia (MD 23.01; CI 11.14, 34.88; I^2 98%; n = 1521) remained.

There are a number of limitations in our review. Firstly, results could potentially be biased by selective reporting and missing outcome data, but the funnel plots were reassuring [17–19,93–100]. Secondly, as the latest pain score was extracted from each time interval there could be significant variation in the timing which may explain some of the statistical heterogenicity in intermediate and late pain scores. Late pain scores varied from 24 hours to four days, with later pain scores less likely to demonstrate statistical significance potentially influencing the results. The variation in timing of recorded postoperative opioid consumption, from one hour to five days, may also account for some of the statistical heterogenicity. Thirdly, results from the high dose and postoperative subgroup analyses should be interpreted with caution given the low numbers available. In addition, we did not investigate the impact of adverse effects of dexamethasone administration as this has previously been done [2,3,101]. However, when reported, adverse features reported were similar between intervention and control groups and not attributed to dexamethasone administration.

Furthermore, pain was the primary outcome in less than half the studies but when analyses were restricted to studies with pain as the primary outcome all results remained statistically significant except late pain scores on movement. In addition, pain scores on movement were less likely to be reported potentially reducing the strength of the sensitivity analyses. Pain scores on movement should be the focus of future studies given the drive for postoperative mobilisation.

Additionally, due to lack of data we were unable to perform our prespecified subgroup analyses GA + CNB and GA + RA. Dexamethasone may impact on postoperative pain in combination with general and regional anaesthesia, but it is unclear if this can be translated to the general surgical population [102–104]. It is our opinion that this question remains unanswered and should guide future research.

Unfortunately, nearly half of all studies were deemed high ROB, frequently due to selection of the reported result with failure to report all measured pain scores. As the majority of studies had a non-pain primary outcome, ROB assessment at study rather than outcome level would have impacted these results. ROB assessment highlighted issues with study methodology, with inadequate allocation concealment in nearly half of all studies, and trialists should be reminded of reporting guidelines for RCTs [105]. Additionally, the type of analysis was infrequently documented, and we judged nearly half of all studies undertook a per-protocol analysis due to exclusions of protocol violations and post-randomisation participants for reasons not pre-specified. Some exclusions are justified in a modified intention-to-treat (mITT) analysis, but we exercised caution using this label due to ambiguity over the definition [106,107]. We feel clarification of mITT criteria is essential to avoid subjectivity of future ROB assessments. However, the completeness of outcome data provides some reassurance over the safety and lack of adverse features of dexamethasone.

In conclusion a single perioperative dose of intravenous dexamethasone reduces early, intermediate and late pain scores both at rest and on movement, opioid requirements and increases time to first analgesia in patients undergoing elective abdominal surgery. Preoperative administration of intermediate dose is likely to have the greatest impact on outcomes.

Abbreviations

CENTRAL Cochrane Central Register of Controlled Trials; CI: Confidence Interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNB: Central Neuraxial Blockade; EMBASE: Exerpta Medica Database; GA: General Anaesthesia; ICTRP: International Clinical Trials Registry Portal; MEDLINE: Medical Analysis and Retrieval System Online; MD: Mean Difference; mITT: modified Intention to Treat; PACU: Post

Anaesthesia Care Unit; PRISMA: preferred reporting items for systematic reviews and meta-analysis; RA: Regional Anaesthesia; RevMan: Review Manager; RCT; Randomised Controlled Trial; ROB: Risk of Bias; PONV: Postoperative Nausea and Vomiting; WHO: World Health Organisation.

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

All data collected and analysed for the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare they have no competing interests.

Funding

Dr S Bampoe is supported by an award from the NIHR UCLH Biomedical Research Centre.

Authors' contributions

CM and SB contributed to the conception and design. CM and SJC contributed to the data collection, data analysis, manuscript writing. COD, SB and DW contributed to the manuscript writing. All authors have read and approved the final manuscript.

Acknowledgements

We would like to thank Mrs. Angela Thompson, Librarian, Queen's University Belfast for her assistance in reviewing the search strategy and Hazel Neale, Healthcare Librarian, Healthcare Library of Northern Ireland at Craigavon Area Hospital, for her assistance in obtaining certain texts.

References

1. Moore SG. Intravenous Dexamethasone as an Analgesic: A Literature Review. AANA Journal. 2018;86(6):488-93.
2. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575-88.
3. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110(2):191-200.
4. Ahn Y, Woods J, Connor S. A systematic review of interventions to facilitate ambulatory laparoscopic cholecystectomy. HPB (Oxford). 2011;13(10):677-86.
5. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg. 2002;195(5):694-712.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
8. Research NIfH. International prospective register of systematic reviews [Internet]. University of York, York, UK.: Centre for Reveiws and Dissemination; 2020 [cited 2020. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=176202.
9. Alexander JI. Pain after laparoscopy. Br J Anaesth. 1997;79(3):369-78.
10. Lefebvre C GJ, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. 2019. In: Cochrane [Internet]. [94 pages]. Available from: www.training.cochrane.org/handbook.
11. World Health Organisation. The ICTRP Search Portal [Internet]. Geneva SWHO. Geneva, Switzerland: World Health Organisation; 2020 [updated 2020 May 29; cited 2020 June 1]. Available from: https://www.who.int/ictrp/search/en/.
12. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

13. Bataille A, Letourneulx JF, Charmeau A, Lemedioni P, Leger P, Chazot T, et al. Impact of a prophylactic combination of dexamethasone-ondansetron on postoperative nausea and vomiting in obese adult patients undergoing laparoscopic sleeve gastrectomy during closed-loop propofol-remifentanil anaesthesia: A randomised double-blind placebo-controlled study. Eur J Anaesthesiol. 2016;33(12):898-905.
14. Jo YY, Lee JW, Shim JK, Lee WK, Choi YS. Ramosetron, dexamethasone, and their combination for the prevention of postoperative nausea and vomiting in women undergoing laparoscopic cholecystectomy. Surg Endosc. 2012;26(8):2306-11.
15. Sanchez-Ledesma MJ, Lopez-Olaondo L, Pueyo FJ, Carrascosa F, Ortega A. A comparison of three antiemetic combinations for the prevention of postoperative nausea and vomiting. Anesth Analg. 2002;95(6):1590-5, table of contents.
16. Ko-Iam W, Sandhu T, Paiboonworachat S, Pongchairerks P, Junrungsee S, Chotirosniramit A, et al. Metoclopramide, versus its combination with dexamethasone in the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy: a double-blind randomized controlled trial. J Med Assoc Thai. 2015;98(3):265-72.
17. Chen Y, Dong C, Lian G, Li D, Yin Y, Yu W, et al. Dexamethasone on postoperative gastrointestinal motility: A placebo-controlled, double-blinded, randomized controlled trial. J Gastroenterol Hepatol. 2020.
18. D'Souza N, Swami M, Bhagwat S. Comparative study of dexamethasone and ondansetron for prophylaxis of postoperative nausea and vomiting in laparoscopic gynecologic surgery. Int J Gynaecol Obstet. 2011;113(2):124-7.
19. Kirdak T, Yilmazlar A, Cavun S, Ercan I, Yilmazlar T. Does single, low-dose preoperative dexamethasone improve outcomes after colorectal surgery based on an enhanced recovery protocol? Double-blind, randomized clinical trial. Am Surg. 2008;74(2):160-7.
20. Higgins JPT LT, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane. 2019.
21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
22. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785-805.
23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
25. Rasmussen LS, Yentis SM, Kawamoto M, Shafer SL, Reilly CS, Miller DR, et al. Joint editors-in-chief request for determination regarding papers published by Dr. Yoshitaka Fujii. 2012 [cited 2020 May 26]. Available from: http://journals.lww.com/greenjournal/Documents/Fujii_Joint_Editorial_Request_ Regarding_Dr_Yoshitaka_Fujii.pdf. .
26. Carlisle JB. The analysis of 168 randomised controlled trials to test data integrity. Anaesthesia. 2012;67(5):521-37.
27. Scott JR. Expression of concern. 2012 [cited 2020 May 26]. Available from: http://journals.lww.com/greenjournal/Documents/ExpressionOfConcern.pdf.
28. Myles PS, Carlisle JB, Scarr B. Evidence for compromised data integrity in studies of liberal peri-operative inspired oxygen. Anaesthesia. 2019;74(5):573-84.
29. Abreu MP, Vieira JL, Silva IF, Miziara LE, Fofano R. [Efficacy of ondansetron, metoclopramide, droperidol and dexametasone in preventing post-gynecological videolaparoscopy nausea and vomiting in outpatient setting. Comparative study.]. Rev Bras Anestesiol. 2006;56(1):8-15.
30. Asadollah S, Vahdat M, Yazdkhasti P, Nikravan N. The influence of dexamethasone on postoperative nausea and vomiting in patients undergoing gynecologic laparoscopic surgeries: A randomised, controlled, double blind trial. Turk J Obstet Gynecol. 2014;11(4):219-23.
31. Lee Y, Lai HY, Lin PC, Huang SJ, Lin YS. Dexamethasone prevents postoperative nausea and vomiting more effectively in women with motion sickness. Can J Anaesth. 2003;50(3):232-7.
32. Ormel G, Romundstad L, Lambert-Jensen P, Stubhaug A. Dexamethasone has additive effect when combined with ondansetron and droperidol for treatment of established PONV. Acta Anaesthesiol Scand. 2011;55(10):1196-205.
33. Rajeeva V BN, Batra Y.K, Dhaliwal L.K. Comparison of ondansetron with ondansetron and dexamethasone in prevention of PONV in diagnostic laparoscopy. Can J Anaesth. 1998;46(1).
34. SS M. Effects of dexamethasone on early postoperative pain, nausea and vomiting and recovery time after ambulatory laparoscopic surgery. J Med Sci. 2007;7(7):1202-05.
35. Thomas R, Jones N. Prospective randomized, double-blind comparative study of dexamethasone, ondansetron, and ondansetron plus dexamethasone as prophylactic antiemetic therapy in patients undergoing day-case gynaecological surgery. Br J Anaesth. 2001;87(4):588-92.
36. De Oliveira GS, Jr., Ahmad S, Fitzgerald PC, Marcus RJ, Altman CS, Panjwani AS, et al. Dose ranging study on the effect of preoperative dexamethasone on postoperative quality of recovery and opioid consumption after ambulatory gynaecological surgery. Br J Anaesth.

2011;107(3):362-71.

37. Kassim D, Esmat I, Elgendy M. Impact of duloxetine and dexamethasone for improving postoperative pain after laparoscopic gynecological surgeries: A randomized clinical trial. Saudi J Anaesth. 2018;12(1):95-102.
38. Rothenberg DM, McCarthy RJ, Peng CC, Normoyle DA. Nausea and vomiting after dexamethasone versus droperidol following outpatient laparoscopy with a propofol-based general anesthetic. Acta Anaesthesiol Scand. 1998;42(6):637-42.
39. Fryar CD K-MD, Gu Q, Ogden CL. Mean body weight, height, waist circumference, and body mass index among adults: United States 1999-2000 through 2015-2016. National Health Statistics Reports. 2018;122:1-16.
40. Lee C, Chung JY, Lee M. Sex-related differences in the efficacy of dexamethasone pretreatment for postoperative analgesia in patients undergoing laparoscopic cholecystectomy: a randomized controlled study. Turk J Med Sci. 2017;47(4):1282-6.
41. Elhakim M, Nafie M, Mahmoud K, Atef A. Dexamethasone 8 mg in combination with ondansetron 4 mg appears to be the optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth. 2002;49(9):922-6.
42. Jokela RM, Ahonen JV, Tallgren MK, Marjakangas PC, Korttila KT. The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. Anesth Analg. 2009;109(2):607-15.
43. Liu K, Hsu CC, Chia YY. The effective dose of dexamethasone for antiemesis after major gynecological surgery. Anesth Analg. 1999;89(5):1316-8.
44. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear T, Vender JS, et al. The effect of single low-dose dexamethasone on blood glucose concentrations in the perioperative period: a randomized, placebo-controlled investigation in gynecologic surgical patients. Anesth Analg. 2014;118(6):1204-12.
45. Thangaswamy CR, Rewari V, Trikha A, Dehran M, Chandralekha. Dexamethasone before total laparoscopic hysterectomy: a randomized controlled dose-response study. J Anesth. 2010;24(1):24-30.
46. Lim SH, Jang EH, Kim MH, Cho K, Lee JH, Lee KM, et al. Analgesic effect of preoperative versus intraoperative dexamethasone after laparoscopic cholecystectomy with multimodal analgesia. Korean J Anesthesiol. 2011;61(4):315-9.
47. Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth Analg. 2000;91(1):136-9.
48. Pajunen P, Vartiainen E, Mannisto S, Jousilahti P, Laatikainen T, Peltonen M. Intra-individual changes in body weight in population-based cohorts during four decades: the Finnish FINRISK study. Eur J Public Health. 2012;22(1):107-12.
49. Areeruk P, Ittichaikulthol W, Termpornlert S, Pravitharangul T, Nganlasom J, Charoensap C, et al. The Effect of a Single Dose Dexamethasone on Postoperative Pain in Patients Undergoing Gynecological Laparotomy Surgery. J Med Assoc Thai. 2016;99(11):1239-44.
50. Bianchin A, De Luca A, Caminiti A. Postoperative vomiting reduction after laparoscopic cholecystectomy with single dose of dexamethasone. Minerva Anestesiol. 2007;73(6):343-6.
51. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg. 2003;238(5):651-60.
52. Coloma M, White PF, Markowitz SD, Whitten CW, Macaluso AR, Berrisford SB, et al. Dexamethasone in combination with dolasetron for prophylaxis in the ambulatory setting: effect on outcome after laparoscopic cholecystectomy. Anesthesiology. 2002;96(6):1346-50.
53. Corcoran T, Paech M, Law D, Muchatuta NA, French M, Ho KM. Intraoperative dexamethasone alters immune cell populations in patients undergoing elective laparoscopic gynaecological surgery. Br J Anaesth. 2017;119(2):221-30.
54. Feo CV, Sortini D, Ragazzi R, De Palma M, Liboni A. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. Br J Surg. 2006;93(3):295-9.
55. Fukami Y, Terasaki M, Okamoto Y, Sakaguchi K, Murata T, Ohkubo M, et al. Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: a prospective randomized double-blind study. J Hepatobiliary Pancreat Surg. 2009;16(3):367-71.
56. Ionescu DC, Hadade AI, Mocan TA, Margarit SD. The influence of a prophylactic dose of dexamethasone for postoperative nausea and vomiting on plasma interleukin concentrations after laparoscopic cholecystectomy: a randomised trial. Eur J Anaesthesiol. 2014;31(4):204-11.
57. Liu K, Hsu CC, Chia YY. Effect of dexamethasone on postoperative emesis and pain. Br J Anaesth. 1998;80(1):85-6.
58. Murphy GS, Szokol JW, Greenberg SB, Avram MJ, Vender JS, Nisman M, et al. Preoperative dexamethasone enhances quality of recovery after laparoscopic cholecystectomy: effect on in-hospital and postdischarge recovery outcomes. Anesthesiology. 2011;114(4):882-90.
59. Olajumoke TO, Afolayan JM, Fashanu AO, Adekunle MA. Single dose of dexamethasone for prevention of nausea and vomiting after major gynaecological surgery. Niger J Med. 2013;22(3):207-11.
60. Pauls RN, Crisp CC, Oakley SH, Westermann LB, Mazloomdoost D, Kleeman SD, et al. Effects of dexamethasone on quality of recovery following vaginal surgery: a randomized trial. Am J Obstet Gynecol. 2015;213(5):718 e1-7.

61. Sanchez-Rodriguez PE, Fuentes-Orozco C, Gonzalez-Ojeda A. Effect of dexamethasone on postoperative symptoms in patients undergoing elective laparoscopic cholecystectomy: randomized clinical trial. World J Surg. 2010;34(5):895-900.
62. Sistla S, Rajesh R, Sadasivan J, Kundra P, Sistla S. Does single-dose preoperative dexamethasone minimize stress response and improve recovery after laparoscopic cholecystectomy? Surg Laparosc Endosc Percutan Tech. 2009;19(6):506-10.
63. Tolver MA, Strandfelt P, Bryld EB, Rosenberg J, Bisgaard T. Randomized clinical trial of dexamethasone versus placebo in laparoscopic inguinal hernia repair. Br J Surg. 2012;99(10):1374-80.
64. Viriyaroj V, Boonsinsukh T, Rookkachart T, Yigsakmongkol N. The Effects of Single-Dose Preoperative Intravenous Dexamethasone on Clinical Outcome after Laparoscopic Cholecystectomy. J Med Assoc Thai. 2015;98 Suppl 10:S112-7.
65. Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth. 1999;83(5):772-5.
66. Wu JI, Lu SF, Chia YY, Yang LC, Fong WP, Tan PH. Sevoflurane with or without antiemetic prophylaxis of dexamethasone in spontaneously breathing patients undergoing outpatient anorectal surgery. J Clin Anesth. 2009;21(7):469-73.
67. Batistaki C, Pandazi A, Kyttari A, Kaminiotis E, Kostopanagiotou G. Is there an interaction between dexamethasone and sugammadex in real clinical conditions? A randomized controlled trial in patients undergoing laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2019;35(2):215-9.
68. Alghanem SM, Massad IM, Rashed EM, Abu-Ali HM, Daradkeh SS. Optimization of anesthesia antiemetic measures versus combination therapy using dexamethasone or ondansetron for the prevention of postoperative nausea and vomiting. Surg Endosc. 2010;24(2):353-8.
69. Bilgin TE, Birbicer H, Ozer Z, Doruk N, Tok E, Oral U. A comparative study of the antiemetic efficacy of dexamethasone, ondansetron, and metoclopramide in patients undergoing gynecological surgery. Med Sci Monit. 2010;16(7):CR336-41.
70. Yuksek MS, Alici HA, Erdem AF, Cesur M. Comparison of prophylactic anti-emetic effects of ondansetron and dexamethasone in women undergoing day-case gynaecological laparoscopic surgery. J Int Med Res. 2003;31(6):481-8.
71. Benevides ML, Oliveira SS, de Aguilar-Nascimento JE. The combination of haloperidol, dexamethasone, and ondansetron for prevention of postoperative nausea and vomiting in laparoscopic sleeve gastrectomy: a randomized double-blind trial. Obes Surg. 2013;23(9):1389-96.
72. Gautam B, Shrestha BR, Lama P, Rai S. Antiemetic prophylaxis against postoperative nausea and vomiting with ondansetron-dexamethasone combination compared to ondansetron or dexamethasone alone for patients undergoing laparoscopic cholecystectomy. Kathmandu Univ Med J (KUMJ). 2008;6(23):319-28.
73. Kasagi Y, Hayashida M, Sugasawa Y, Kikuchi I, Yamaguchi K, Okutani R, et al. Antiemetic effect of naloxone in combination with dexamethasone and droperidol in patients undergoing laparoscopic gynecological surgery. J Anesth. 2013;27(6):879-84.
74. Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth. 1996;76(6):835-40.
75. Maddali MM, Mathew J, Fahr J, Zarroug AW. Postoperative nausea and vomiting in diagnostic gynaecological laparoscopic procedures: comparison of the efficacy of the combination of dexamethasone and metoclopramide with that of dexamethasone and ondansetron. J Postgrad Med. 2003;49(4):302-6.
76. Nesek-Adam V, Grizelj-Stojcic E, Rasic Z, Cala Z, Mrsic V, Smiljanic A. Comparison of dexamethasone, metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Surg Endosc. 2007;21(4):607-12.
77. Pan PH, Lee SC, Harris LC. Antiemetic prophylaxis for postdischarge nausea and vomiting and impact on functional quality of living during recovery in patients with high emetic risks: a prospective, randomized, double-blind comparison of two prophylactic antiemetic regimens. Anesth Analg. 2008;107(2):429-38.
78. Ryu JH, Chang JE, Kim HR, Hwang JW, Oh AY, Do SH. Ramosetron vs. ramosetron plus dexamethasone for the prevention of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy: prospective, randomized, and double-blind study. Int J Surg. 2013;11(2):183-7.
79. Shrestha BB, Karmacharya M, Gharti BB, Timilsina B, Ghimire P. Effect of Dexamethasone and Pheniramine Maleate in Patients Undergoing Elective Laparoscopic Cholecystectomy. JNMA J Nepal Med Assoc. 2014;52(195):920-4.
80. McKenzie R, Riley TJ, Tantisira B, Hamilton DL. Effect of propofol for induction and ondansetron with or without dexamethasone for the prevention of nausea and vomiting after major gynecologic surgery. J Clin Anesth. 1997;9(1):15-20.
81. Regasa T, Aweke Z, Neme D, Hailu S, Jemal B, Mekonen S. Comparison of prophylactic dexamethasone, metoclopramide, and combination of dexamethasone and metoclopramide for prevention of post-operative nausea and vomiting for major gyanecological surgery in Hawassa university compressive specialized hospital, Ethiopia, 2019. International Journal of Surgery Open. 2020;27:18-24.
82. Hammas B, Thorn SE, Wattwil M. Superior prolonged antiemetic prophylaxis with a four-drug multimodal regimen - comparison with propofol or placebo. Acta Anaesthesiol Scand. 2002;46(3):232-7.

83. Badawy AA, Sakka AE. Preoperative gabapentin alone or in combination with dexamethasone on postoperative pain relief after abdominal hysterectomies. A randomized controlled trial. Egyptian Journal of Anaesthesia. 2015;31(2):107-13.
84. Kurz A, Fleischmann E, Sessler DI, Buggy DJ, Apfel C, Akca O, et al. Effects of supplemental oxygen and dexamethasone on surgical site infection: a factorial randomized trialdouble dagger. Br J Anaesth. 2015;115(3):434-43.
85. Mathiesen O, Rasmussen ML, Dierking G, Lech K, Hilsted KL, Fomsgaard JS, et al. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand. 2009;53(2):227-35.
86. Samad K, Khan M, Hameedullah, Khan FA, Hamid M, Khan FH. Unplanned prolonged postanaesthesia care unit length of stay and factors affecting it. J Pak Med Assoc. 2006;56(3):108-12.
87. De Oliveira GS, Jr., Castro-Alves LJ, Ahmad S, Kendall MC, McCarthy RJ. Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials. Anesth Analg. 2013;116(1):58-74.
88. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. World J Surg. 2019;43(3):659-95.
89. Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019;29(4):651-68.
90. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr. 2012;31(6):801-16.
91. Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg. 2016;40(9):2065-83.
92. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesth Analg. 2020;131(2):411-48.
93. Bala I, Bharti N, Murugesan S, Gupta R. Comparison of palonosetron with palonosetron-dexamethasone combination for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiol. 2014;80(7):779-84.
94. Bilgin TE, Birbicer H, Doruk N, Altunkan A, Camdeviren H, Akca O, et al. The role of dexamethasone on postoperative nausea and vomiting after gynaecological surgery: a double-blind placebo controlled comparative study with ondansetron and metoclopramide.: *European Journal of Anaesthesiology*; 2004. p. 18.
95. Chu CC, Shieh JP, Tzeng JI, Chen JY, Lee Y, Ho ST, et al. The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy. Anesth Analg. 2008;106(5):1402-6, table of contents.
96. Karaman K, Bostanci EB, Aksoy E, Ulas M, Yigit T, Erdemli MO, et al. Effects of dexamethasone and pheniramine hydrogen maleate on stress response in patients undergoing elective laparoscopic cholecystectomy. Am J Surg. 2013;205(2):213-9.
97. McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth Analg. 1994;79(5):961-4.
98. Ramesh M KP. Role of dexamethasone in acute postoperative pain, nausea and vomiting in patients undergoing laparoscopic gynocoological surgeries as day case procedures. 2011. p. 725-6.
99. Wang JJ, Ho ST, Uen YH, Lin MT, Chen KT, Huang JC, et al. Small-dose dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy: a comparison of tropisetron with saline. Anesth Analg. 2002;95(1):229-32, table of contents.
100. Zargar-Shoshtari K, Sammour T, Kahokehr A, Connolly AB, Hill AG. Randomized clinical trial of the effect of glucocorticoids on peritoneal inflammation and postoperative recovery after colectomy. Br J Surg. 2009;96(11):1253-61.
101. Polderman JA, Farhang-Razi V, Van Dieren S, Kranke P, DeVries JH, Hollmann MW, et al. Adverse side effects of dexamethasone in surgical patients. Cochrane Database Syst Rev. 2018;11:CD011940.
102. Chen Q, An R, Zhou J, Yang B. Clinical analgesic efficacy of dexamethasone as a local anesthetic adjuvant for transversus abdominis plane (TAP) block: A meta-analysis. PLoS One. 2018;13(6):e0198923.
103. Fan Z, Ma J, Kuang M, Zhang L, Han B, Yang B, et al. The efficacy of dexamethasone reducing postoperative pain and emesis after total knee arthroplasty: A systematic review and meta-analysis. Int J Surg. 2018;52:149-55.
104. Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Database Syst Rev. 2017;11:CD011770.
105. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;63(8):e1-37.
106. Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. BMJ. 2010;340:c2697.
107. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res. 2011;2(3):109-12.

Figures

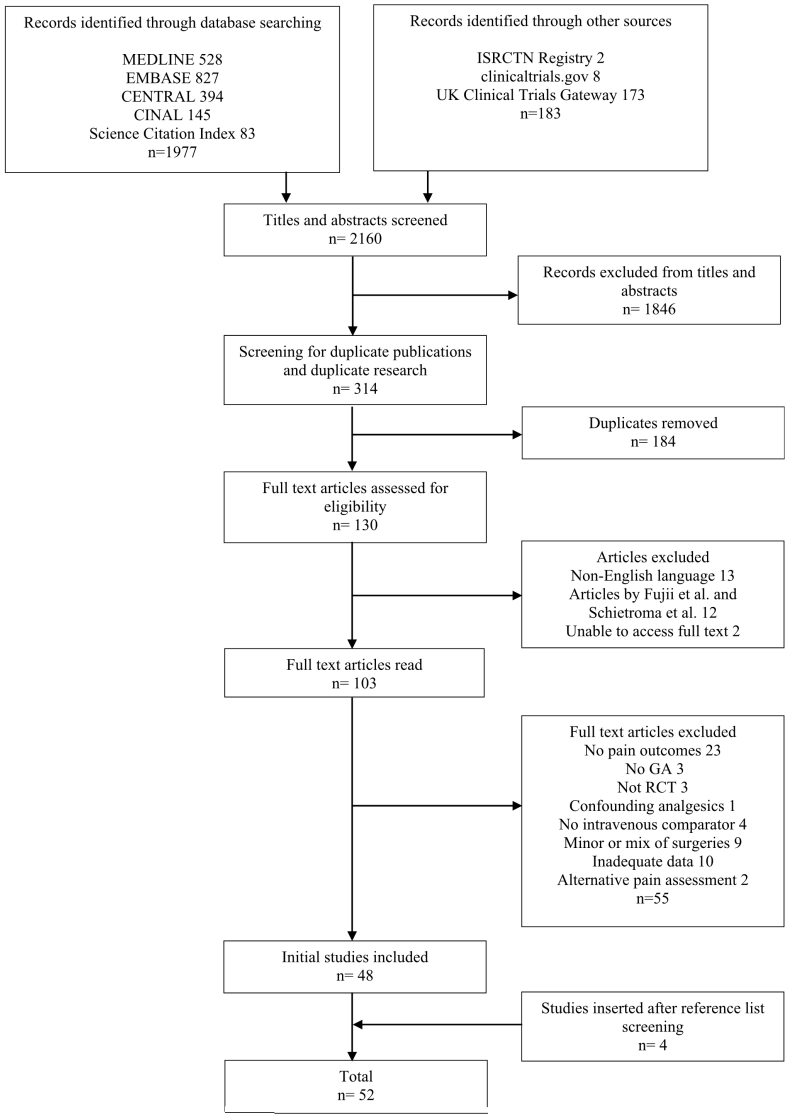

Figure 1

PRISMA flow diagram detailing process of study selection.

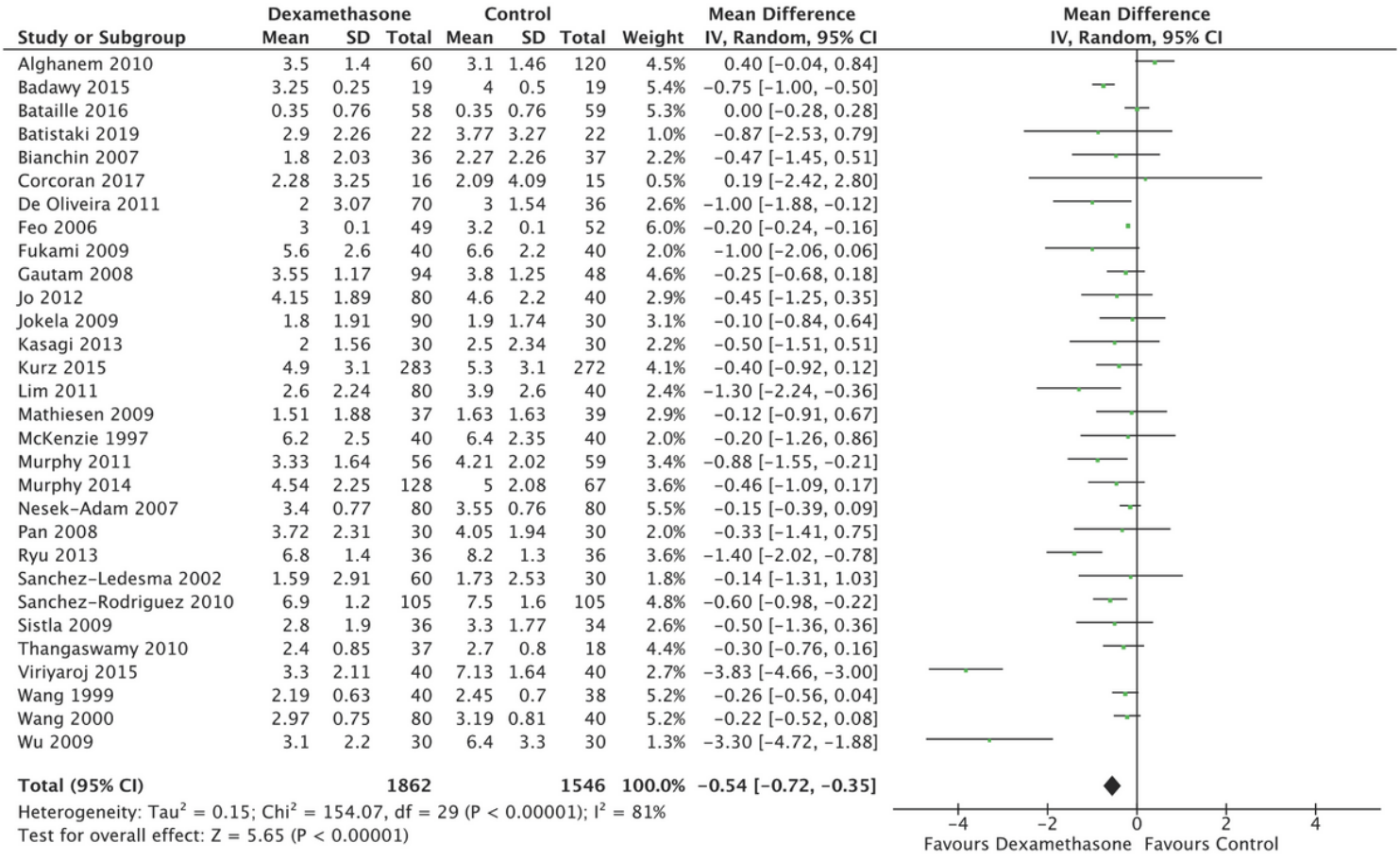

Figure 2

Forest plot for early (≤4 hours) VAS pain scores at rest.

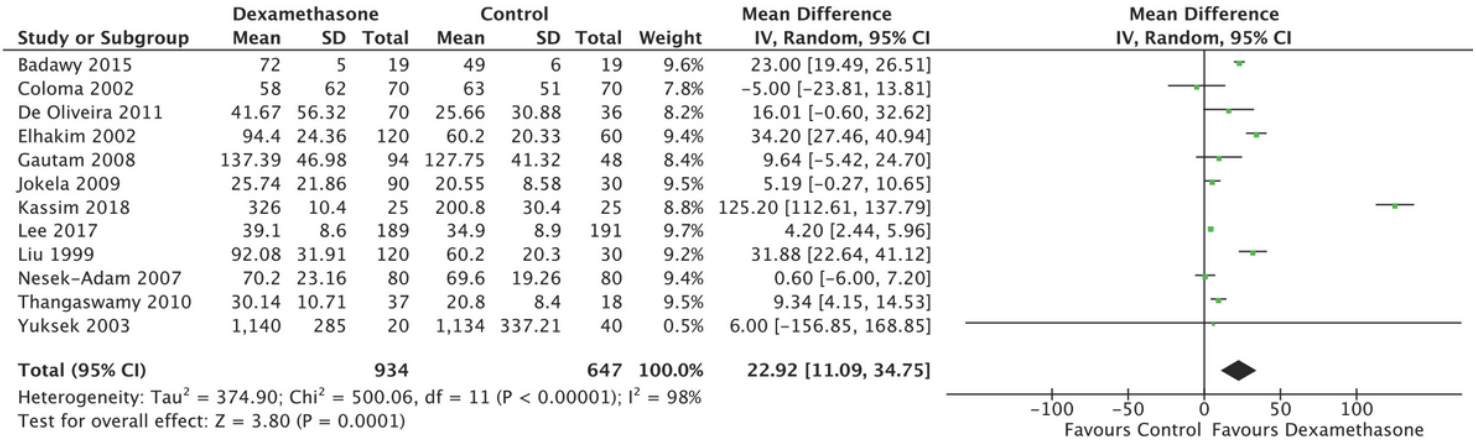

Figure 3

Forest plot for time to first analgesia in minutes.

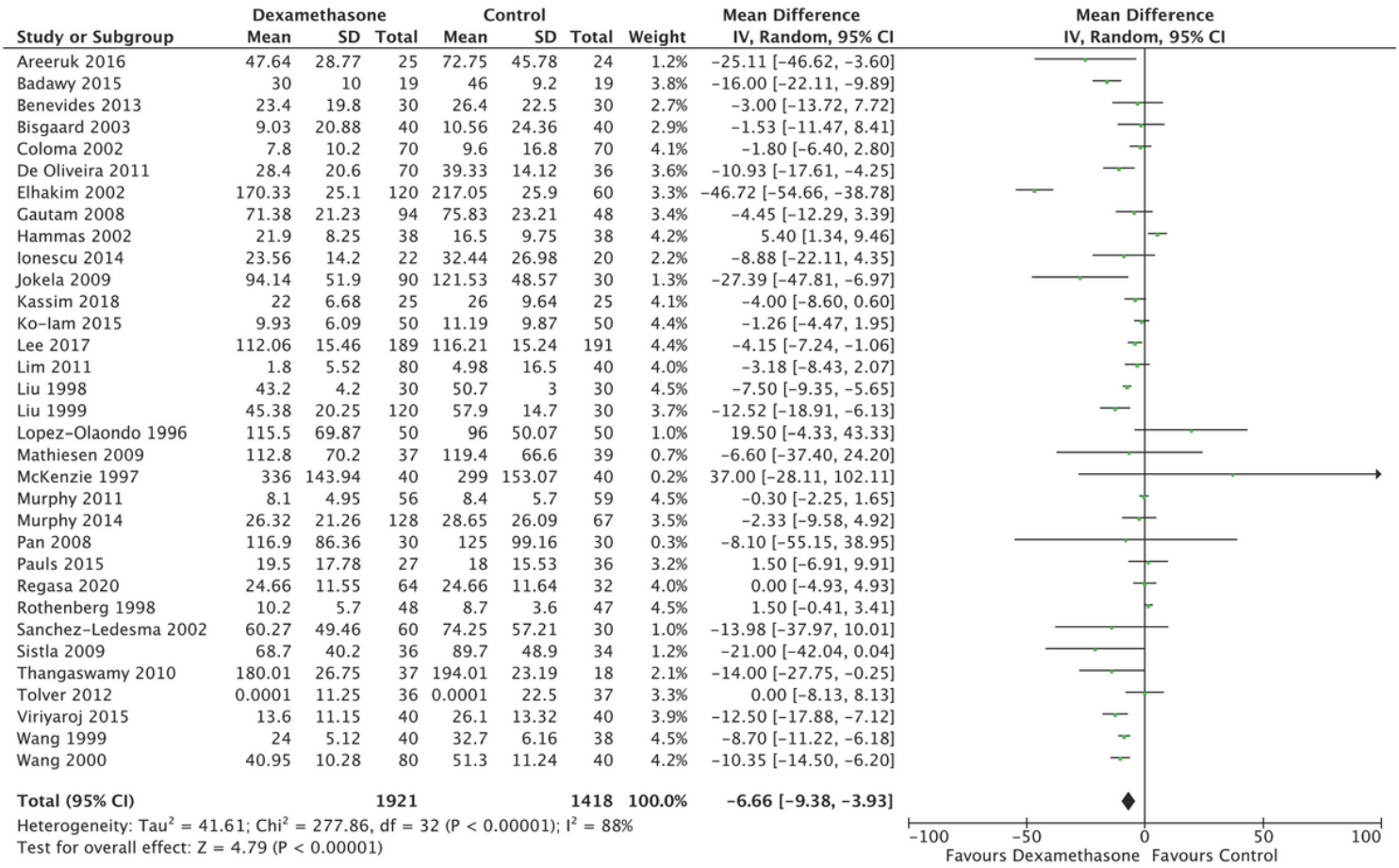

Figure 4

Forest plot for total postoperative opioid use in mg of oral morphine equivalents.

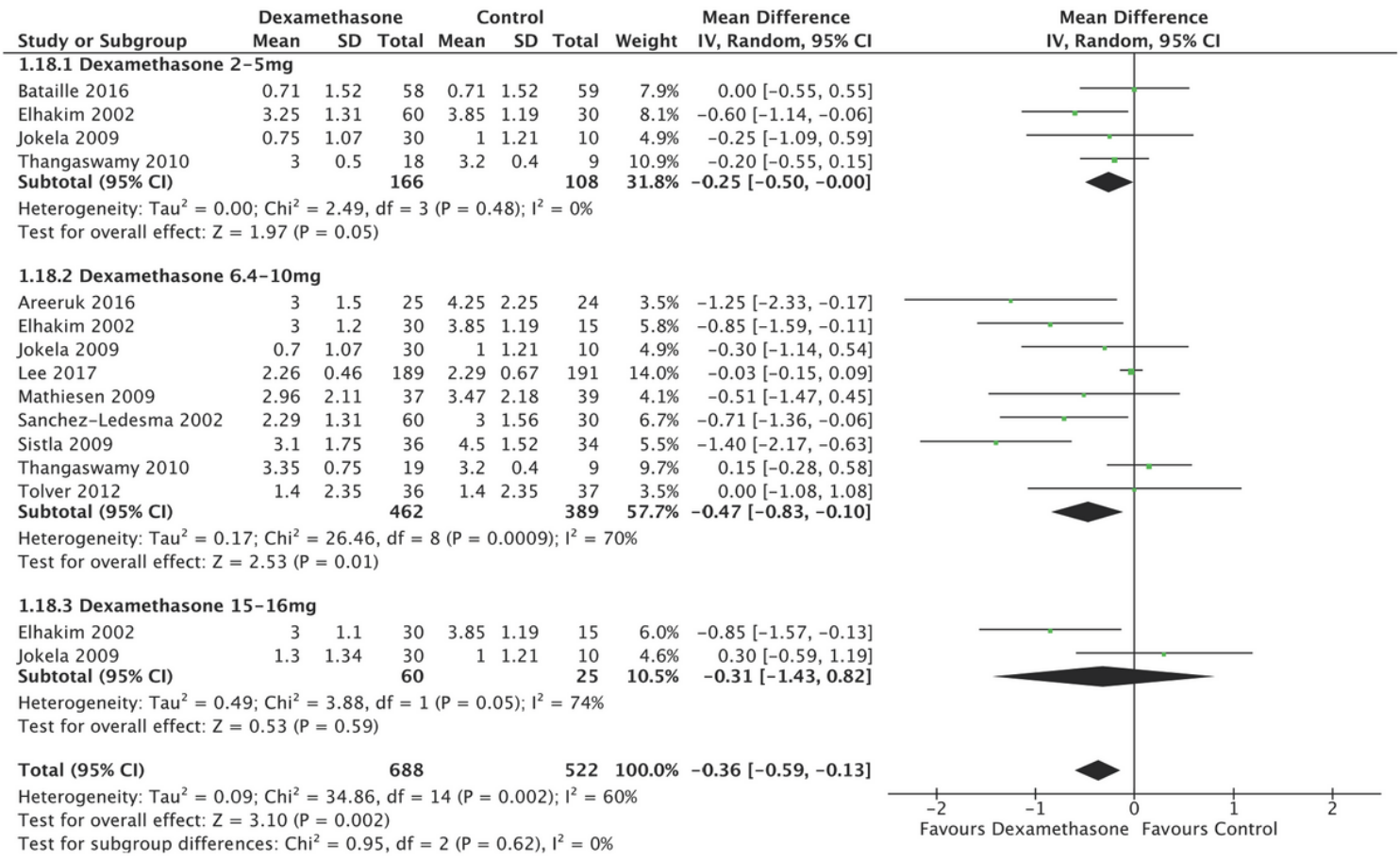

Figure 5

Forest plot for dexamethasone dosing late (≥24 hours) VAS pain scores at rest.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile4.docx
- AdditionalFile6.docx
- AdditionalFile7.docx
- Additionalfile1.docx
- Additionalfile2.docx
- Additionalfile3.docx
- Additionalfile5.docx