

# Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis

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## Editor's key points

- Dexamethasone appears to have some analgesic effects in the postoperative period.
- Meta-analysis of 45 studies found lower pain scores and lower opioid requirement at 2 and 24 h.
- While the effect was statistically significant, the clinical benefit is less clear.
- Blood glucose was raised after operation, but there was no apparent increase in adverse effects.

**Background.** The analgesic efficacy and adverse effects of a single perioperative dose of dexamethasone are unclear. We performed a systematic review to evaluate the impact of a single i.v. dose of dexamethasone on postoperative pain and explore adverse events associated with this treatment.

**Methods.** MEDLINE, EMBASE, CINAHL, and the Cochrane Register were searched for randomized, controlled studies that compared dexamethasone vs placebo or an antiemetic in adult patients undergoing general anaesthesia and reported pain outcomes.

**Results.** Forty-five studies involving 5796 patients receiving dexamethasone 1.25–20 mg were included. Patients receiving dexamethasone had lower pain scores at 2 h {mean difference (MD) –0.49 [95% confidence interval (CI): –0.83, –0.15]} and 24 h [MD –0.48 (95% CI: –0.62, –0.35)] after surgery. Dexamethasone-treated patients used less opioids at 2 h [MD –0.87 mg morphine equivalents (95% CI: –1.40 to –0.33)] and 24 h [MD –2.33 mg morphine equivalents (95% CI: –4.39, –0.26)], required less rescue analgesia for intolerable pain [relative risk 0.80 (95% CI: 0.69, 0.93)], had longer time to first dose of analgesic [MD 12.06 min (95% CI: 0.80, 23.32)], and shorter stays in the post-anaesthesia care unit [MD –5.32 min (95% CI: –10.49 to –0.15)]. There was no dose–response with regard to the opioid-sparing effect. There was no increase in infection or delayed wound healing with dexamethasone, but blood glucose levels were higher at 24 h [MD 0.39 mmol litre<sup>–1</sup> (95% CI: 0.04, 0.74)].

**Conclusions.** A single i.v. perioperative dose of dexamethasone had small but statistically significant analgesic benefits.

**Keywords:** analgesics, opioid; dexamethasone; glucocorticoids; hyperglycaemia; pain, postoperative; surgical wound infection

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Glucocorticoids have been used to reduce inflammation and tissue damage in a variety of conditions, including inflammatory bowel disease, rheumatoid arthritis, and some malignancies. Glucocorticoids have potent immunomodulatory effects, and are used in the treatment of acute allograft rejection. They also have antiemetic properties and dexamethasone is commonly used for the prevention of postoperative nausea and vomiting (PONV).<sup>1–3</sup>

The efficacy of glucocorticoids for reducing pain and inflammation after surgery has recently been explored. Early studies in patients undergoing dental procedures showed that glucocorticoids were effective in reducing postoperative pain and oedema.<sup>4–6</sup> A number of recent studies have investigated the potential analgesic benefit of a single perioperative dose of dexamethasone but have inconsistent findings.<sup>7–12</sup>

Long-term treatment with glucocorticoids is associated with many side-effects.<sup>13</sup> However, it is unclear if a single

perioperative dose of dexamethasone increases the risk of these adverse effects. This is due to many of the published studies being underpowered to detect clinically relevant side-effects,<sup>2</sup> and many studies also excluded patients at the highest risk of glucocorticoid-related adverse effects.<sup>1</sup>

We therefore performed this systematic review to determine if a single perioperative dose of dexamethasone in adult surgical patients undergoing surgery under general anaesthesia has a useful analgesic effect in the postoperative period. We also investigated whether the use of dexamethasone increases the risk of postoperative adverse effects.

## Methods

We followed the recommendations of the PRISMA statement in creating this review.<sup>14</sup> The databases of MEDLINE (1966–2011), EMBASE, CINAHL, and the Cochrane Register of

Controlled Trials were searched without language restrictions to identify full reports of randomized, controlled trials in which a single i.v. dose of dexamethasone was given peri-operatively to adult patients undergoing surgery under general anaesthesia and was compared with either placebo or another antiemetic agent. Keywords used in the search included 'dexamethasone', 'steroids', 'corticosteroids', 'glucocorticoids', 'pain', 'postoperative pain', 'nausea', 'vomiting', 'postoperative nausea and vomiting', and 'surgery'. In addition, the references of included studies and related systematic reviews were manually searched for additional relevant studies. Trials were required to report pain outcomes such as pain scores, analgesic consumption, administration of rescue analgesics, or time to first dose of analgesic. Trials were included if they measured pain as either a primary or secondary outcome. Studies in which patients received intrathecal or epidural local anaesthetics or opioids were excluded. In addition, studies using high doses of dexamethasone (>20 mg) were excluded. We also excluded studies involving dental/endodontic procedures, as there is a recently published review on this subject.<sup>15</sup> Data from abstracts, letters to the editor, retrospective trials, and case reports were not included. We did not include the studies by Fujii and colleagues<sup>16</sup> due to concern about the validity of their data, and the recommendation to exclude their work from further scientific consideration.<sup>17</sup> The date of the last search was May 25, 2011.

Three authors (T.K.A., C.A.J., N.H.W.) independently conducted a comprehensive literature search to identify relevant studies. All authors examined each title and abstract to exclude clearly irrelevant articles. At least two authors (T.K.A., C.A.J., A.S.H., N.H.W.) extracted data independently. Any disagreements were resolved by discussion between two reviewers, with a third reviewer available for arbitration if necessary.

Articles meeting the inclusion criteria were scored independently by two authors (N.H.W., C.A.J.) for methodological validity using the four-item, seven-point modified Oxford scale.<sup>18</sup> Any discrepancies were resolved by discussion with a third author (A.S.H.). The minimum score of an included trial was 3 and the maximum was 7.

The data were entered into a data collection form that included the following: (i) type of surgery, (ii) number of patients, (iii) dose(s) of dexamethasone, (iv) comparator(s), (v) timing of administration, (vi) primary outcome measure of study (PONV vs postoperative pain), (vii) outcome measures including pain scores, analgesic consumption, need for rescue analgesia, time to first analgesic request, and time in post-anaesthesia care unit (PACU), and (viii) side-effects related to dexamethasone administration, including wound infection, delayed wound healing, hyperglycaemia, and perineal pruritus. Attempts were made to contact the authors of original papers when additional data were required. Data were extracted from figures as needed if not displayed numerically and authors did not respond to our request to supply numerical data.

In studies evaluating different doses of dexamethasone or more than one comparator, the data from all doses and comparators were pooled for analysis. Pain scores documented at the early (2 h after the end of surgery) and late (24, 48, and 72 h after the end of surgery) postoperative periods were included for analysis. When pain scores were reported at different time points, those reported within 1 h of our defined time points were included in the analysis. Pain intensity scores were assumed to be at rest unless otherwise noted. Pain scores reported using the 0–100 mm visual analogue scale (VAS) were converted to the 11-point (0–10; 0, no pain, and 10, worst possible pain) scale.

All postoperative opioid consumption was converted to morphine equivalents using the table included in Supplementary Appendix S1. In addition, ketorolac dosages were converted to morphine equivalents.<sup>19</sup> Opioid consumption was analysed for the early (2 h) and late (24 h) postoperative periods. When opioid consumption was reported at different time points, reported data within 1 h of our defined time points were included in the analysis. One study reported mean opioid consumption in milligrams per kilogram.<sup>20</sup> This was converted to total milligrams using 70 kg as the patients' average weight based upon data from the National Public Health Institute of Finland, where this study was performed.<sup>21</sup> In papers using the median, range, or both as a measure of central tendency, an attempt was made to contact the author and secure group data as mean and standard deviation. When this was not possible, the median, range, or both were converted to the mean, standard deviation, or both.<sup>22</sup>

## Meta-analysis

Analyses were performed using the Review Manager (RevMan) Software Version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008) and Comprehensive Meta Analysis software (Version 2.2.050). For continuous data, mean differences (MD) with 95% confidence interval (CI) were calculated. If the 95% CI included 0, we assumed that the difference between dexamethasone and control was not statistically significant. Dichotomous data were analysed using relative risk (RR) with 95% CI. If the 95% CI around the RR did not include 1.0, we assumed that the difference between the dexamethasone and the control groups was statistically significant. For combined data, a random effects model was used by default. Data were graphically plotted using forest plots to evaluate treatment effects. Statistical heterogeneity was assessed using the  $I^2$  test.

In addition to the main analysis (dexamethasone vs control), a number of sensitivity analyses were performed on the primary outcomes of 24 h pain scores and opioid consumption. Data were analysed according to the primary outcome of included studies (pain vs PONV), procedure type (laparoscopic vs open abdominal vs middle ear), and control group (saline vs other antiemetics). We also performed a

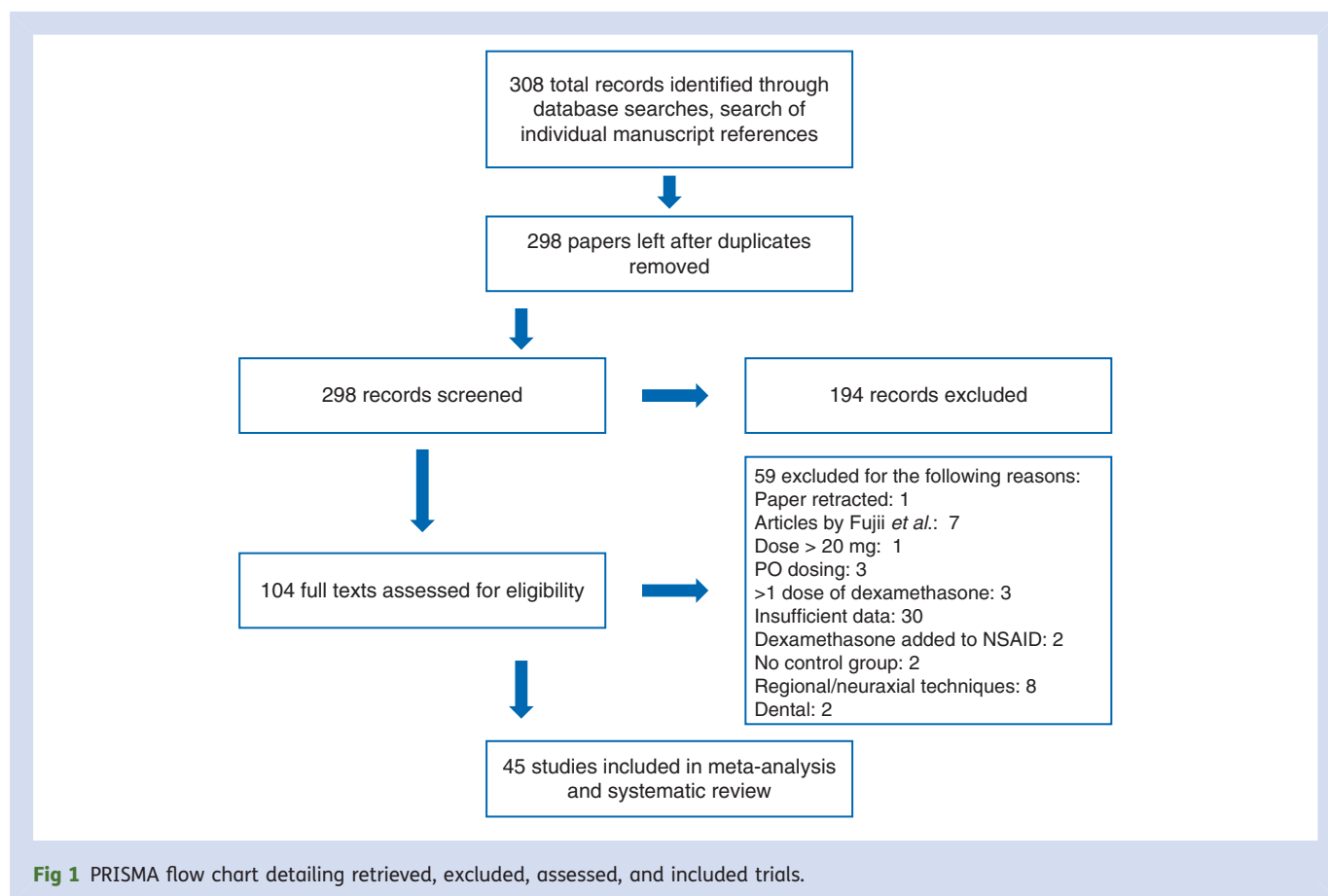
subgroup analysis comparing preoperative vs intraoperative administration of dexamethasone. Publication bias was assessed for the primary outcomes using funnel plots and the regression test described by Egger and colleagues.<sup>23</sup> To assess whether there was dose–response for the analgesic efficacy of dexamethasone, we performed a random effects meta-regression in which the outcome variables were the MD in 24 h morphine consumption or 24 h pain scores with the predictor variable being dexamethasone dose in both analyses. To further assess for a dose–response relationship, we performed a subgroup analysis comparing 24 h opioid consumption and 24 h pain scores with doses of 4–5 and 8–10 mg. Subgroup analyses were performed using a Q-test for heterogeneity across subgroups.

## Results

A total of 308 publications were identified. Of those, 45 studies were included in this review (Supplementary Table S1) giving a total of 5796 patients (2997 who received dexamethasone and 2799 who did not). The PRISMA flow diagram detailing the disposition of retrieved publications is shown in Figure 1. Dexamethasone alone or in combination with a serotonin (5-HT<sub>3</sub>) receptor antagonist, haloperidol, metoclopramide, or midazolam was considered the study drug. Doses of dexamethasone ranged from 1.25 to 20 mg, with 8 mg being the most common dose used. Five studies

included multiple doses of dexamethasone,<sup>11 12 20 24 25</sup> and 38 studies had at least one group that received only dexamethasone.<sup>7–12 20 25–55</sup> Nine studies had at least one group that received dexamethasone in combination with a serotonin (5-HT<sub>3</sub>) receptor antagonist.<sup>24 47 50 56–61</sup> Two studies included a group that received dexamethasone and midazolam,<sup>48 55</sup> one study included a group that received both metoclopramide and dexamethasone,<sup>49</sup> and another included a group that received both haloperidol and dexamethasone.<sup>46</sup> Dexamethasone was given before operation in 28 studies<sup>7–12 20 24 25 27 28 30–34 36 38 39 41–44 47 48 51 56 59</sup> and intraoperatively in 18.<sup>26 29 35 37 40 42 45 46 49 50 52–55 57 58 60 61</sup> One study<sup>42</sup> randomized patients to receive dexamethasone either before operation or intraoperatively.

For the purpose of this analysis, normal saline, serotonin (5-HT<sub>3</sub>) receptor antagonists, butyrophenones, and metoclopramide were categorized as the control (comparator) group. Of the included studies, 31 compared dexamethasone with a placebo group, while 21 studies included a comparator other than saline including 5-HT<sub>3</sub> antagonists,<sup>10 24 45 47 50 52–54 56–61</sup> droperidol,<sup>12 46 51</sup> metoclopramide,<sup>10 49</sup> midazolam,<sup>48 55</sup> and haloperidol.<sup>46</sup> Seven studies had pain as their primary outcome,<sup>11 20 27–29 39 40</sup> while 35 studies had PONV as the primary outcome.<sup>7–10 12 24 25 30–36 38 41–58 60 61</sup> In two studies, both pain and PONV were primary outcomes.<sup>26 37</sup> One study used another measure (a global quality of recovery scale) as its primary outcome.<sup>59</sup> There was considerable



variation in the method of opioid administration between studies. Of the 19 studies<sup>7 8 11 12 20 24 25 30 33 34 39 41 42 47 54 56 57 59 60</sup> in which opioid analgesic requirement was quantified at either 2 or 24 h after operation, approximately half (10 studies) used PRN analgesic dosing, while the other half used patient-controlled analgesia.

## Pain scores

Nineteen studies (2040 patients) recorded VAS pain scores at rest 2 h after operation (Fig. 2).<sup>8 11 12 26 27 31 32 36–39 41 42 44 47 58–61</sup> Patients receiving dexamethasone had significantly lower VAS pain scores at rest at 2 h [MD  $-0.49$  (95% CI:  $-0.83, -0.15$ ,  $P=0.005$ ) ( $I^2=94\%$ )].

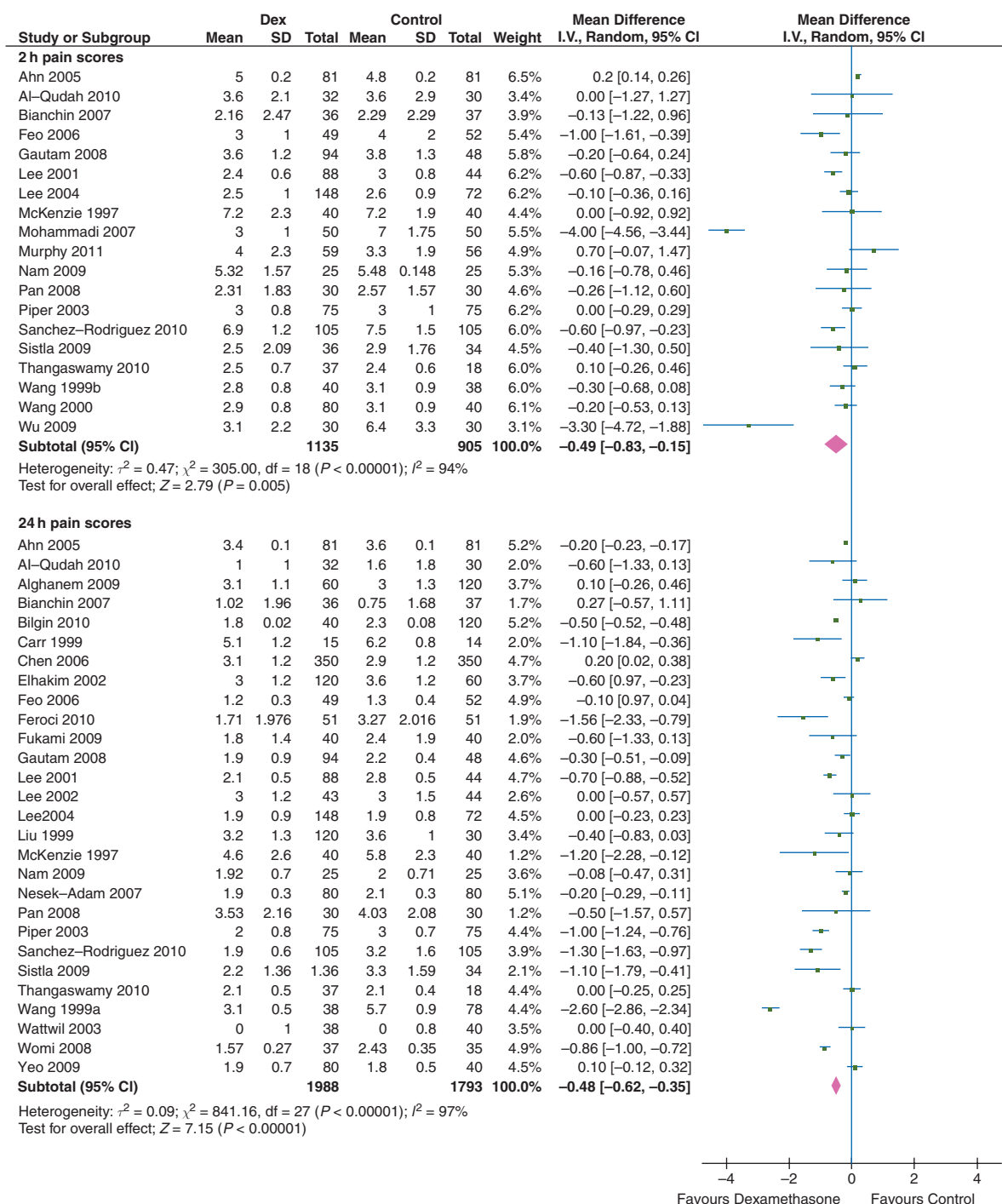


Fig 2 Forest plot for pain scores (VAS) at 2 and 24 h.

Two studies (125 patients) recorded VAS pain scores with movement 2 h after operation.<sup>11 39</sup> There was no significant reduction in pain scores in patients receiving dexamethasone [MD -0.15 (95% CI: -0.95, 0.64,  $P=0.70$ ) ( $I^2=60\%$ )].

Twenty-eight studies (3781 patients) recorded VAS pain scores at 24 h after operation (Fig. 2).<sup>7-12 24-27 29-33 37-39 43 45 47 49 51 54 55 58 60 61</sup> Patients receiving dexamethasone had significantly lower VAS pain scores at 24 h [MD -0.48 (95% CI: -0.62, -0.35,  $P<0.00001$ ) ( $I^2=97\%$ )]. This result did not differ by restricting the analysis to studies with pain<sup>11 26 27 29 37 39</sup> [MD -0.32 (95% CI: -0.57, -0.07,  $P=0.01$ ) ( $I^2=69\%$ )] or PONV<sup>7-10 12 24-26 30-33 37 38 43 45 47 49 51 54 55 58 60 61</sup> [MD -0.48 (95% CI: -0.62, -0.33,  $P<0.00001$ ) ( $I^2=97\%$ )] as a primary outcome. Restricting the analysis to dexamethasone compared with saline also did not alter this effect [MD -0.42 (95% CI: -0.54 to -0.29,  $P<0.00001$ ) ( $I^2=95\%$ )]. There was evidence of dose responsiveness with respect to the 24 h pain scores [slope (95% CI)=-0.041 (-0.078, -0.005),  $P=0.026$ ]. When the two studies using dexamethasone 20 mg were removed, there was no further evidence of dose responsiveness [slope (95% CI)=-0.034 (-0.078, 0.011),  $P=0.139$ ]. Subgroup analysis of 24 h pain scores also showed no difference between doses of 4-5 and 8-10 mg ( $P=0.12$ ).

Patients who received dexamethasone reported significantly lower VAS pain scores at 24 h after laparoscopic surgery<sup>8 9 11 24 31 37-39 45 47 49 60</sup> [MD -0.33 (95% CI: -0.53, -0.13,  $P=0.001$ ) ( $I^2=83\%$ )], but not after open abdominal surgery<sup>25 58</sup> [MD -0.64 (95% CI: -1.36, 0.08,  $P=0.08$ ) ( $I^2=46\%$ )] or middle ear surgery<sup>26 55</sup> [MD -0.07 (95% CI: -0.36, 0.22,  $P=0.64$ ) ( $I^2=86\%$ )]. Subgroup analysis showed a statistically significant difference between pre-operative and intraoperative administration of dexamethasone ( $P=0.03$ ). The reduction in 24 h VAS scores was greater when dexamethasone was given before operation [MD -0.59 (95% CI: -0.83, -0.35,  $P<0.00001$ ) ( $I^2=96\%$ )] compared with intraoperatively [MD -0.27 (95% CI: -0.45, -0.10) ( $P<0.002$ ,  $I^2=86\%$ )].

Four studies<sup>11 24 39 49</sup> (465 patients) recorded VAS with movement at 24 h after surgery. Patients receiving dexamethasone had significantly lower VAS pain scores [MD -0.49 (95% CI: -0.84, -0.13,  $P=0.007$ ) ( $I^2=84\%$ )]. Visual inspection of the funnel plot (Fig. 3) and Egger's regression intercept suggests that there was no evidence of publication bias [intercept=-0.54 (95% CI: -2.87, 1.80) ( $P=0.64$ )].

Six studies (393 patients) recorded VAS pain scores at 48 h after operation.<sup>7 9 29 37 43 60</sup> Patients receiving dexamethasone had significantly lower VAS pain scores at 48 h [MD -0.35 (95% CI: -0.47, -0.24,  $P<0.00001$ ) ( $I^2=4\%$ )]. In addition, the pooled results of three studies (169 patients)<sup>9 29 60</sup> which measured pain scores at 72 h after operation did not show a reduction in pain scores with dexamethasone [MD -0.35 (95% CI: -0.72, 0.02,  $P=0.07$ ) ( $I^2=0\%$ )].

### Opioid use

Nine studies (978 patients) recorded opioid use at 2 h after operation (Fig. 4).<sup>11 12 20 39 41 42 57 59 60</sup> Patients receiving dexamethasone used significantly less opioids (mg morphine equivalents) [MD -0.87 (95% CI: -1.40 to -0.33,  $P=0.002$ ) ( $I^2=52\%$ )]. This represents a 13.0% decrease in pooled opioid consumption compared with control. Fourteen studies (2157 patients) recorded opioid use at 24 h after operation (Fig. 4).<sup>7 8 11 12 20 24 25 30 33 34 39 47 54 56</sup> Patients receiving dexamethasone used significantly less opioid in the first 24 h after surgery [MD -2.33 (95% CI: -4.39, -0.26,  $P=0.03$ ) mg morphine equivalents ( $I^2=98\%$ )]. This represents a 10.3% reduction in opioid consumption compared with controls. There was no evidence of dose responsiveness with respect to this outcome [slope (95% CI)=-0.169 (-0.693, 0.355),  $P=0.526$ ]. Subgroup analysis also showed no difference between doses of 4-5 and 8-10 mg ( $P=0.93$ ). The primary outcome of the study did modulate this effect; in studies having pain as the primary outcome, patients receiving dexamethasone used significantly less opioids [MD -2.70 (95% CI: -3.40, -2.00,  $P<0.00001$ ) mg

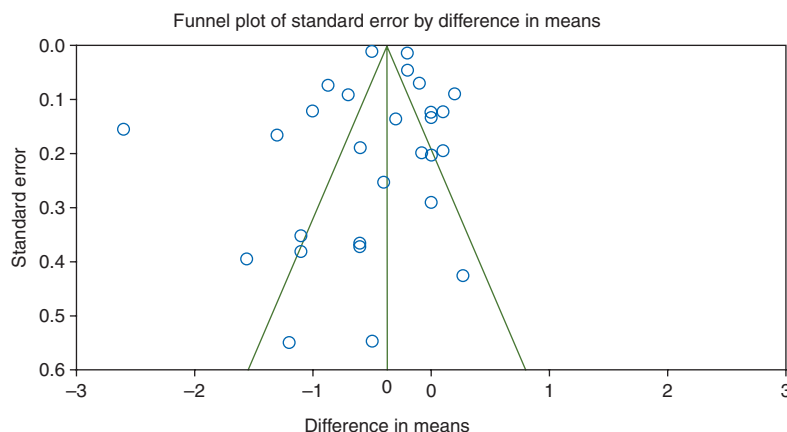


Fig 3 Funnel plot for pain scores (VAS) at 24 h.



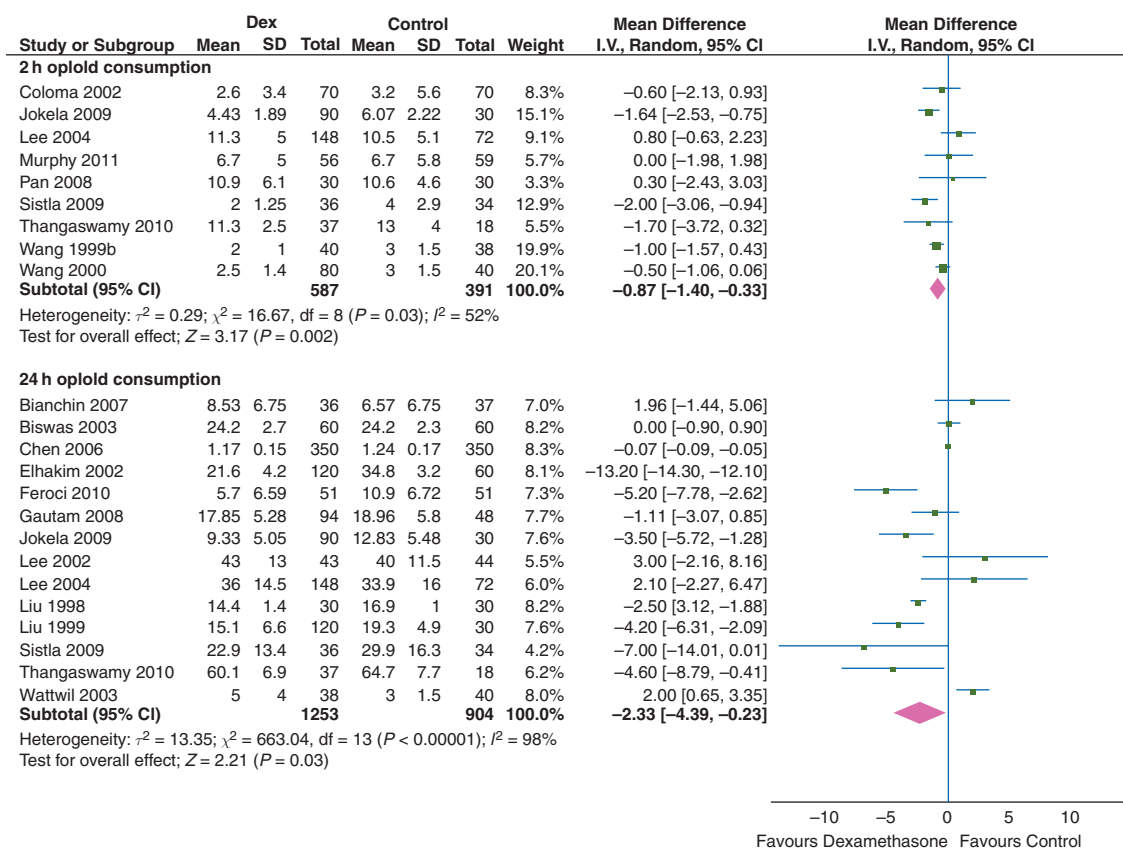


Fig 4 Forest plot for opioid use (mg of morphine equivalents) at 2 and 24 h.

morphine equivalents ( $I^2=3\%$ ), but studies with PONV as the primary outcome showed no significant difference in opioid use. Restricting the analysis to dexamethasone vs saline groups did not alter this effect [MD -1.96 (95% CI: -3.52, -0.40,  $P=0.01$ ) mg morphine equivalents ( $P=0.01$ ,  $I^2=92\%$ )].

Procedure type affected this outcome, but in contrast to pain scores, patients after laparoscopic surgery showed no difference in opioid consumption [MD -3.86 (95% CI: -9.29, 1.56,  $P=0.16$ ) mg morphine equivalents ( $I^2=98\%$ )], but after open abdominal surgery, dexamethasone was associated with significantly less opioid consumption [MD -3.04 (95% CI: -4.59, -1.49,  $P=0.0001$ ) mg morphine equivalents ( $I^2=56\%$ )]. Studies in which dexamethasone was given before operation showed a significantly lower opioid consumption at 24 h [MD -2.70 (95% CI: -4.92, -0.47,  $P=0.02$ ) mg morphine equivalents ( $I^2=98\%$ )]. The one study that gave dexamethasone intraoperatively<sup>54</sup> found no difference in opioid consumption at 24 h. Visual inspection of the funnel plot (Fig. 5) and Egger's regression intercept suggest that there was no evidence of publication bias [intercept = -2.92 (95% CI: -6.74, 0.89) ( $P=0.12$ )].

### Rescue analgesic use

Nineteen studies (2230 patients) recorded the use of rescue analgesics for intolerable pain.<sup>9 10 27-29 31 35 36 40 44 46 48-52 55 57</sup>

Patients treated with dexamethasone required less rescue analgesia [RR 0.80 (95% CI: 0.69, 0.93,  $P=0.004$ ) ( $I^2=35\%$ )].

### Time to first analgesic dose

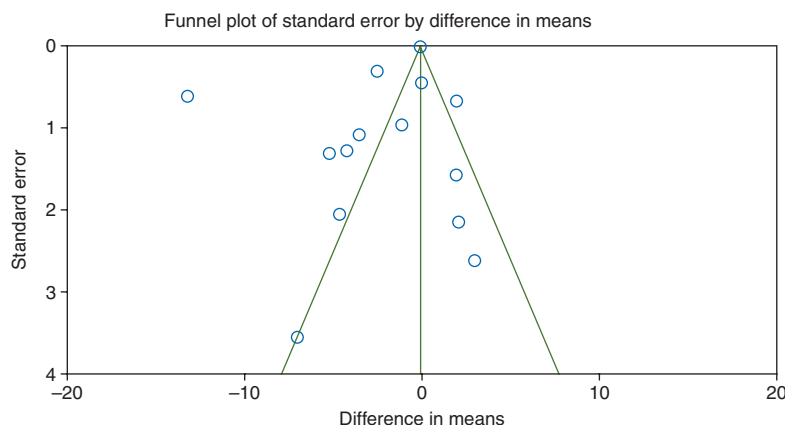
Seven studies (947 patients) recorded the time to first dose of analgesic.<sup>11 20 24 25 47 49 57</sup> Patients treated with dexamethasone had a significantly longer time to first dose of analgesic [MD 12.06 (95% CI: 0.80, 23.32,  $P=0.04$ ) min ( $I^2=94\%$ )].

### Time to PACU discharge

Eight studies (810 patients) examined the time to PACU discharge.<sup>11 28 36 44 55 57 59 60</sup> Patients receiving dexamethasone had significantly shorter stays in PACU [MD -5.32 (95% CI: -10.49, -0.15,  $P=0.04$ ) min ( $I^2=77\%$ )].

### Adverse events

Fourteen studies (1449 patients) reported the incidence of infection.<sup>8 9 11 26 28 31-33 35 38 40 43 55 59</sup> Eleven found no infections in either dexamethasone-treated or placebo patients. In the three remaining studies (235 patients), there was no increase in infection in patients receiving dexamethasone [RR 0.63 (95% CI: 0.23, 1.69,  $P=0.36$ ) ( $I^2=0\%$ )]. Nine studies (1020 patients) examined the incidence of delayed healing.<sup>8 11 26 31-33 35 38 55</sup> Seven studies found no delayed



**Fig 5** Funnel plot for opioid use (mg of morphine equivalents) at 24 h.

healing in either dexamethasone-treated or placebo patients. In the two remaining studies (283 patients), there was no increased risk of delayed healing in patients receiving dexamethasone [RR 1.27 (95% CI: 0.32, 4.96,  $P=0.73$ ) ( $I^2=0\%$ )]. Three studies measured perioperative blood glucose in non-diabetic patients.<sup>7 11 31</sup> All measured blood glucose <12 h after operation (258 patients), and two<sup>7 31</sup> measured blood glucose 24 h after operation (203 patients). At <12 h after operation, no conclusions could be made due to wide CIs of the pooled results [MD 0.64 mmol litre<sup>-1</sup> (95% CI: -0.23, 1.52,  $P=0.15$ ) ( $I^2=89\%$ )]. At 24 h after operation, blood sugar in the dexamethasone group was significantly higher [MD 0.39 mmol litre<sup>-1</sup> (95% CI: 0.04, 0.74,  $P=0.03$ ) ( $I^2=10\%$ )]. Two studies<sup>30 49</sup> measured the incidence of perineal pruritus after dexamethasone. In one study,<sup>49</sup> dexamethasone was given after induction of anaesthesia, and therefore no perineal pruritus was found, but when dexamethasone<sup>30</sup> was given 1 min before induction, 55% reported perineal pruritus, with a 4:1 female:male ratio.

## Discussion

In this meta-analysis, patients treated with dexamethasone experienced less postoperative pain, required less postoperative opioids, had longer time to first analgesic dose, needed less rescue analgesia, and had shorter PACU stays. Differences between the groups were however small and may not be clinically relevant. There was no evidence of a dose-response relationship with regard to the effect of dexamethasone on 24 h morphine consumption. Although we observed some evidence of dose responsiveness with respect to the 24 h pain scores, the parameter estimates were so small that they are likely to be of minimal clinical significance. These effects were not accompanied by an increased risk of infection or delayed wound healing. Patients treated with dexamethasone had significantly higher blood glucose levels during the first postoperative day.

Reductions in pooled opioid consumption with dexamethasone were modest, with reductions of ~13% and 10% at 2 and 24 h, respectively, and possibly not clinically relevant. Studies in which PONV was the primary outcome showed no difference between patients receiving dexamethasone and control, whereas pain studies showed around 3 mg difference in 24 h morphine equivalent requirement (8.7% reduction in opioid use). Patients having laparoscopic surgery showed no difference in opioid consumption, but after open abdominal surgery, there was a 3 mg (16.8%) morphine reduction in the first 24 h.

The onset of dexamethasone is thought to be 1–2 h allowing time to diffuse across the cell membrane and alter gene transcription.<sup>62</sup> Administration of steroids 60 min or more before surgical trauma may be important in minimizing pain and inflammation.<sup>2</sup> Similarly, dexamethasone is a more effective antiemetic when given before induction of anaesthesia than at the end of surgery.<sup>42</sup> In our analysis, preoperative administration was more effective than intraoperative administration in reducing 24 h pain scores, but the difference was small and may not be clinically relevant.

Similar to others,<sup>1 2 63</sup> we found no increase in infection associated with steroid administration. However, patients at higher risk of infection are often excluded from perioperative studies of dexamethasone.<sup>1</sup> Patients receiving dexamethasone had small but statistically significant elevations in blood glucose at 24 h after operation. A single perioperative dose of dexamethasone has been shown to elevate intraoperative blood glucose for 4 h.<sup>64</sup> In another study, more profound elevations in blood glucose after dexamethasone were associated with higher BMI and higher baseline HbA1c.<sup>65</sup> We found that this hyperglycaemic period after dexamethasone extends to the first 24 h after operation. While hyperglycaemia is known to adversely affect patient outcome after cardiac surgery<sup>66</sup> and subarachnoid haemorrhage,<sup>67</sup> it is unclear whether the hyperglycaemia found in our analysis has any clinical implications.

Overall, our findings agree with those of a recent review<sup>68</sup> on the same topic, but our analysis included more than double the number of study patients. We did not restrict the analysis to placebo comparisons but included patients treated with antiemetics. Our sensitivity analysis showed that restricting the analysis to placebo-treated patients did not change results. In addition, our paper includes a number of sensitivity analyses and outcomes not examined before, including rescue analgesic use, early opioid use, and pain >24 h after operation. The previous analysis<sup>68</sup> examined a dose–effect relationship of dexamethasone by deriving a milligram per kilogram dose and dividing the studies into low (<0.10 mg kg<sup>-1</sup>), intermediate (0.11–0.20 mg kg<sup>-1</sup>), or high (>0.21 mg kg<sup>-1</sup>) dose dexamethasone, then performing pairwise subgroup analyses. They found that intermediate and high dose but not low-dose dexamethasone reduced 24 h opioid consumption compared with placebo, and the reduction with intermediate and high doses was statistically higher than low dose. There were only four studies in the low-dose group and there were no head-to-head comparisons between low dose and higher doses, only comparisons with placebo. We instead opted to utilize meta-regression using doses reported in the initial studies to test for the presence of a dose–effect relationship. We also performed subgroup analysis using commonly used antiemetic doses (4–5 vs 8–10 mg). We did not find a dose–response relationship for this effect. We believe that the approach of creating subgroups based on a milligram per kilogram dose has limitations. First, the mean weight of the patients in those studies was used, and not the individual patient data. Secondly, for articles where weight was not reported, a mean weight of 70 kg was used, potentially introducing inaccuracies.

A limitation of our review is the variability in the type of surgery, dexamethasone dose and timing, anaesthetic regimen, type of postoperative rescue analgesic, and reported outcomes resulting in the heterogeneity seen in many of the studied outcomes. This heterogeneity was reduced or eliminated in some of the subgroup analyses by only including studies with pain as the primary outcome, or by performing the analysis according to the type of surgery. Another potential limitation is that we pooled antiemetics and placebo groups as a collective control group. Some studies have suggested that metoclopramide<sup>69 70</sup> and ondansetron<sup>71</sup> may have analgesic properties, but others have not supported this.<sup>10 24 45 49</sup> Overall, the results were not changed if only saline or other antiemetics were used as comparators. Studies also utilized various postoperative analgesic regimens. In addition, outcome measures were not uniform across studies, making meta-analysis challenging. In some cases, presentation of data was unsatisfactory, with results reported only as figures. Most studies had PONV as the primary outcome, with pain being the primary endpoint in only seven studies. In addition, the duration of most studies was limited to 24 h with very few reporting beyond 24 h after operation or the occurrence of chronic pain. Finally,

many studies had small sample sizes, and did not investigate or report the occurrence of adverse events.

The antiemetic effect of dexamethasone is well known,<sup>1 3</sup> and therefore was not analysed in this review. While the mechanism of the antiemetic effect of dexamethasone is unclear, opioid sparing and lower pain may contribute to less PONV.<sup>72 73</sup> It could be argued that the analgesic effect of a single dose of dexamethasone observed in this review is small and not clinically relevant. However, since dexamethasone has a useful antiemetic effect, it does enhance postoperative recovery and may justify its use in surgical patients.

In summary, we found that perioperative single-dose dexamethasone was associated with small but statistically significant reductions in postoperative pain, postoperative opioid consumption, need for rescue analgesia, PACU stays, and a longer time to first analgesic dose. The effect on postoperative opioid consumption was not dose-dependent. In addition, we found no increased risk of infection or delayed wound healing, although dexamethasone was associated with slight hyperglycaemia on the first postoperative day. There is a need for studies of dexamethasone in which pain is the primary outcome. In addition, dose-ranging studies and studies in patients at higher risk for glucocorticoid-induced complications are required.

## Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

## Declaration of interest

None declared.

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