Benefits and Risks of Dexamethasone in Noncardiac Surgery

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Dexamethasone is a commonly used drug in anesthesia and surgery. The purported beneficial effects are diverse, especially for the prophylaxis and treatment of postoperative nausea and vomiting, but the optimal dose and the clinical implications of potential side effects require an updated summary of all available evidence.

This article reviews major trials and other studies of perioperative dexamethasone in adult noncardiac surgery, focusing on patient selection, optimal dose, and safety. We briefly consider its mode(s) of action and central role in the management of postoperative nausea and vomiting before providing updates on the benefits of dexamethasone for postoperative pain, quality of recovery, fatigue, sleep disturbance and mood, major complications and death, surgical site infection, hyperglycemia and diabetes control, and perioperative neurocognitive disorders, and conclude with a consideration of the optimal dexamethasone dose. We will not consider its use in pediatrics, cardiac surgery, or as a perineural adjuvant in peripheral nerve blocks.

In 2020, Weibel *et al.* published their results of an extensive systematic review and network meta-analysis comparing the clinical effect and safety of antiemetic drugs in adults undergoing any type of surgery under general anesthesia.[1] The authors concluded that effectiveness for postoperative nausea and vomiting has been convincingly demonstrated *but* that additional studies were needed to properly investigate the potential adverse effects of dexamethasone, including in patients with diabetes.[1] Such information has now become available.

Mode(s) of Action

The mechanism of action of dexamethasone for postoperative nausea and vomiting is poorly understood, but it is likely to result from both nongenomic and genomic anti-inflammatory actions.[2–6] Surgery typically includes tissue injury and induces an inflammatory response,[7,8] both of which result in postoperative pain. Corticosteroids have potent anti-inflammatory actions that likely mitigate these effects,[2] presumably *via* their inhibition of both the cyclooxygenase and the lipoxygenase pathways,[3,9] stabilization of neuronal membranes[10] and spinal cord nociceptive processing,[11] and reduction of bradykinin concentration in tissue.[12] Dexamethasone has also been shown to suppress the release of neuropeptides such as calcitonin gene–related peptide and substance P from nerve endings after tissue injury.[13]

The effects of IV dexamethasone take approximately 1 to 2 h to manifest because it needs to cross cell membranes in order to alter gene transcription.[3] Thus, it should be administered postinduction but before the start of surgery.[14] Because dexamethasone has a rather long biologic half-life of 36 to 72 h, a single dose can suppress cortisol concentration for up to 1 week.[4] Glucocorticoids such as dexamethasone can prevent the primary neurohumoral stress defenses from overshooting into dysregulated states that might otherwise impair recovery.[3]

Postoperative Nausea and Vomiting

Postoperative nausea and vomiting is common, troublesome, costly,[14] and is often of greater concern to patients than postoperative pain.[15] It impairs quality of recovery,[16,17] particularly if severe or persistent,[18] and adversely affects patient satisfaction.[19,20] It is more common in nonsmokers,[14] females,[14,21] younger age groups[14,21]; those with a history of motion sickness or previous postoperative nausea and vomiting[14]; patients undergoing abdominal, laparoscopic, or thyroid surgery[14,17,21–23]; and patients with predicted high opioid requirements,[14] as well as after nitrous oxide administration[14,21,24] or longer durations of inhalational anesthesia.[17,21]

The 2013 American Society of Anesthesiologists Practice Guidelines for postanesthetic care stated that dexamethasone "is effective in the prophylaxis of postoperative vomiting and reduced use of rescue antiemetics, for the prophylaxis of nausea when higher doses are administered, and for the treatment of postoperative vomiting (Category A1-B evidence)."[25] The largest randomized trial conducted up until that time was the International Multicenter Protocol to Assess the Single and Combined Benefits of Antiemetic Interventions in a Controlled Clinical Trial, which enrolled 5,199 surgical patients and compared 4 mg

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IV ondansetron, 4 mg dexamethasone, 1.25 mg droperidol, and three anesthetic drug options, in multiple combinations that allowed estimation of individual and combined clinical effects.[26] Dexamethasone reduced the risk of postoperative nausea and vomiting by 26% (relative risk [RR], 0.74 [95% CI, 0.70 to 0.82]; $P < 0.001$), comparable to both ondansetron and droperidol. Any combination of two of these drugs reduced the risk of postoperative nausea and vomiting by 45%. Dexamethasone is thus a first-line option for both the prevention and treatment of postoperative nausea and vomiting.[14] It can be used alone or in combination with one or two other classes of antiemetic drugs.[14,26]

The DREAMS (Dexamethasone Reduces Emesis after Major Gastrointestinal Surgery) trial, published in 2017,[22] was a large, pragmatic, multicenter randomized trial conducted across 45 hospitals in the United Kingdom. The enrollment was 1,350 adult patients undergoing elective open or laparoscopic bowel surgery. Participants were randomly assigned to a single dose of 8 mg IV dexamethasone at induction of anesthesia compared with standard care. All patients underwent general anesthesia and otherwise could receive antiemetic prophylaxis (other than dexamethasone) intraoperatively according to the attending anesthesiologist's usual practice. The primary endpoint of early (0 to 24 h) postoperative vomiting occurred in 172 (26%) participants in the dexamethasone group and 223 (33%) in the control group (RR, 0.77 [95% CI, 0.65 to 0.92]; $P = 0.003$). This protective effect was seen across different patient characteristics and analgesic techniques. Patients in the dexamethasone group also required fewer postoperative antiemetics for up to 72 h.[22] Early feeding occurred more often in the dexamethasone group, and there was no evidence of increased risk of superficial surgical site infection or other complications.

The Cochrane systematic review and network meta-analysis by Weibel *et al.* had a special emphasis on the safety of antiemetic drugs.[1] Adverse effects of interest included wound infection, extrapyramidal symptoms, sedation, constipation, headache, QT interval prolongation, and arrhythmias. The network meta-analyses design allowed both direct and indirect comparisons of different drugs across the variety of trial combinations, resulting in multiple one-on-one comparisons while also evaluating multiple treatments. This is a more efficient approach to synthesizing and summarizing all available evidence in a single program of work.[1] They included 585 randomized trials enrolling 97,516 patients, evaluating 44 single drugs and 51 drug combinations, of which dexamethasone was directly compared against comparators in up to 120 of those trials.[1] Intraoperative dexamethasone halved the risk of postoperative vomiting (RR, 0.51 [95% CI, 0.44 to 0.57]). Overall, dexamethasone was found to be highly effective and probably safe, although the authors noted their conclusions about safety were "low certainty" because of insufficient trial data.

The most up-to-date and comprehensive evidence supporting the antiemetic effectiveness and safety of dexamethasone comes from the PADDI (Perioperative Administration of Dexamethasone and Infection) trial, a large, pragmatic, randomized trial enrolling 8,725 patients undergoing noncardiac surgeries with durations of at least 2 h.[27] A single dose of 8 mg IV dexamethasone resulted in a highly significant reduction in the incidence of postoperative nausea and vomiting, even when there was no restriction on the use of other antiemetic therapies (fig. 1). The incidence of any postoperative nausea and vomiting up to 24 h after surgery was 42% in the dexamethasone group and 54% in the placebo group (RR, 0.78 [95% CI, 0.75 to 0.82]; $P < 0.001$). The need for postoperative antiemetic therapy was 38% in the dexamethasone group and 48% in the placebo group ($P < 0.001$).

Postoperative Pain

Given that corticosteroids have potent effects on local inflammatory mediators and pain pathways,[2,3,9–12] it is no surprise that dexamethasone has analgesic properties. Most research into the analgesic benefits of corticosteroids has occurred in dental and maxillofacial surgery. A meta-analysis conducted in 2010 showed a significant decrease in edema and postprocedure pain (both $P < 0.001$) in this setting.[28]

In 2013, a systematic review and meta-analysis of 45 randomized trials that enrolled 5,796 patients was published, evaluating dexamethasone and reported pain outcomes in adults undergoing surgery.[29] Patients undergoing dental and maxillofacial surgery were excluded because of the previous publication.[28] Doses of dexamethasone ranged from 1.25 to 20 mg.[29] Patients receiving dexamethasone had lower pain scores at 2 and 24 h after surgery, but the mean difference in pain scores was approximately 0.5 on a 0-to-10 visual analog scale. Dexamethasone also reduced opioid consumption at both time points, but the small effect size of these benefits suggest minimal clinical value. Importantly, however, dexamethasone-treated patients required less rescue analgesia for intolerable pain (RR, 0.80 [95% CI, 0.69 to 0.93]; $P = 0.004$).[29] The authors could not identify a dose–response with regard to the opioid-sparing effect, but few trials have been done to assess this aspect of corticosteroid pharmacology.

The most recent meta-analysis of trials evaluating numerous adjuvant analgesics, including dexamethasone, was published in 2018.[30] This study included a meta-regression analysis for the outcome of 24-h morphine consumption as a measure of the intensity of analgesic requirements as a baseline covariate to allow the construction of a league table of adjuvant analgesics adjusted for the intensity of surgery. The study included 344 randomized trials enrolling 28,130 patients. The actual type of surgery was not independently associated with analgesic benefit. Many adjuvants had moderate analgesic effects (opioid-sparing effect greater than 10 mg morphine equivalents): gabapentin,

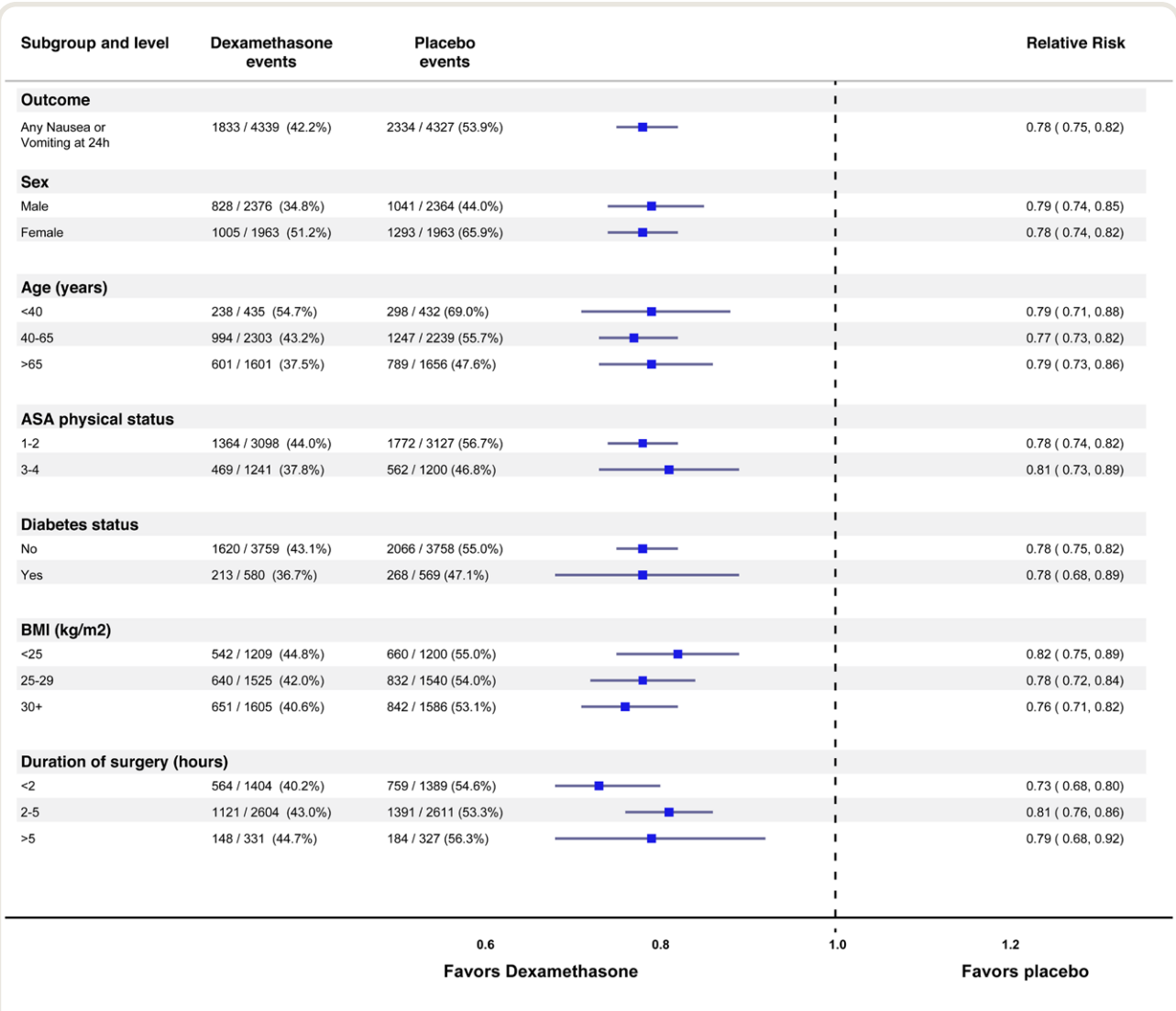

Fig. 1. The effect of 8 mg dexamethasone on the incidence of nausea and vomiting up to 24 h after surgery across subgroups. ASA, American Society of Anesthesiologists; BMI, body mass index.

acetaminophen, α_2-agonists, nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, pregabalin, tramadol, magnesium, and lidocaine. However, dexamethasone had a smaller benefit (approximately 5 mg morphine equivalents).[30] A more recent systematic review found no clinically significant analgesic benefits for gabapentinoids, but did identify a greater risk of adverse events.[31] Dexamethasone has been found to have stronger analgesic benefit in both spine and ear, nose, and throat surgeries.[30] Comparably stronger analgesic benefit has also been identified in a meta-analyses of dexamethasone and other corticosteroids in patients undergoing joint arthroplasty,[32] knee arthroscopy,[33] and tonsillectomy.[34] It seems, therefore, that dexamethasone has useful analgesic properties in some types of surgery, and may also be helpful for patients at risk of opioid-related side effects.

Quality of Recovery, Fatigue, Sleep Disturbance, and Mood

The proinflammatory and catabolic state that occurs after surgery can impair recovery. Wound pain or other discomfort, fatigue, sleep disturbance, and cognitive dysfunction are common.[16] Several validated quality of recovery (QoR) scales have been developed to quantify these and other attributes, along with global scores of recovery.[16,35,36] Some of these QoR scales have been used to evaluate postoperative outcome benefits of dexamethasone.

A small randomized trial published in 2003 found that dexamethasone had likely benefits in patients undergoing laparoscopic cholecystectomy.[37] A dose of 8 mg IV dexamethasone significantly reduced postoperative concentrations of C-reactive protein (an inflammatory marker;

$P = 0.01$), fatigue ($P = 0.01$), overall pain ($P < 0.05$), postoperative nausea and vomiting ($P < 0.05$), and opioid requirements ($P < 0.05$) after surgery.[37] Resumption of recreational activities was significantly faster in the dexamethasone group *versus* placebo group (median, 1 day *vs.* 2 days; $P < 0.05$).[37] The reduction in fatigue and improvement in physical functioning are of particular interest, supporting additional benefits of corticosteroids beyond reductions in postoperative nausea and vomiting and pain.

A double-blind, randomized trial enrolling 106 female patients undergoing outpatient gynecological laparoscopy compared IV saline (control group), 0.05 mg/kg dexamethasone, or 0.1 mg/kg dexamethasone administered immediately before induction of anesthesia.[38] The primary outcome was the global QoR-40 score at 24 h after surgery. Dexamethasone resulted in much improved QoR, with the global median (interquartile range) QoR-40 after 0.1 mg/kg dexamethasone (193 [192 to 195]) being greater than 0.05 mg/kg dexamethasone (179 [175 to 185]; $P = 0.004$) or saline (171 [160 to 182]; $P < 0.005$). The improvement in QoR-40 score seen with the higher dose (0.1 mg/kg) is clinically important.[39] Dexamethasone also provided a clinically important opioid-sparing effect, with the median morphine equivalents administered before discharge being 2.7 mg (0 to 6.3) after 0.1 mg/kg dexamethasone, 5.3 mg (2.4 to 8.8) after 0.05 mg/kg dexamethasone, and 5.3 mg (2.7 to 7.8) after saline ($P = 0.02$). Hospital discharge time was 30 min shorter after 0.1 mg/kg dexamethasone compared with saline ($P = 0.005$). At 24 h, subjects receiving 0.1 mg/kg dexamethasone had consumed less opioid analgesics, and reported less sore throat, muscle pain, confusion, difficulty in falling asleep, and nausea compared with 0.05 mg/kg dexamethasone or saline.[38] Similar findings have been reported by others,[40,41] and in patients undergoing cardiac surgery.[42]

Mihara *et al.* published a sequential analysis of randomized trials in 2016, reporting the clinical benefit of corticosteroids in patients undergoing general anesthesia and surgery assessed using the QoR-40 scale.[41] They identified three randomized trials that enrolled 301 patients and found that dexamethasone significantly improved QoR-40 scores at postoperative day 1 when compared with placebo, with a mean difference of 14.2 points (95% CI, 10.4 to 18.1; $P < 0.001$). Once again, this effect size indicates a clinically important benefit.[39] The positive effects of dexamethasone were most apparent in the dimensions of physical comfort, emotional state, and pain relief.

The PADDI trial also collected QoR data at 24 h and 30 days after surgery.[43] A single dose of 8 mg IV dexamethasone resulted in a moderate improvement in the QoR-15 score at 24 h (median difference, 5.0 [95% CI, 3.8 to 6.2]; $P < 0.001$) when compared with placebo.

These studies offer useful guidance on the optimal dose of dexamethasone in surgery. Although both 4 mg and 8 mg have consistently been shown to provide effective prophylaxis (and treatment) for postoperative nausea and vomiting, the higher dose (8 mg) almost certainly provides additional benefits for both analgesia and QoR, and perhaps earlier hospital discharge.

Major Complications and Death

An excessive (dysregulated) inflammatory response to surgery can lead to organ injury, serious complications, and death. The PACMAN (Perioperative Administration of Corticotherapy on Morbidity and Mortality after Noncardiac Surgery) trial was a pragmatic, double-blind, randomized trial that enrolled 1,222 patients undergoing major noncardiac surgery and compared IV saline (control group) with 0.2 mg/kg IV dexamethasone administered immediately after surgery, with a second 0.2 mg/kg dose administered on the day after surgery.[44] The primary outcome was a composite of postoperative complications or all-cause mortality up to 14 days after surgery. Although the dexamethasone group had less serious complications or death (17.0% *vs.* 19.9%), which was not statistically significant (odds ratio [OR], 0.81 [95% CI, 0.60 to 1.08]; $P = 0.15$), dexamethasone did result in a reduced risk of complications or death in patients undergoing nonthoracic surgery (OR, 0.70 [95% CI, 0.50 to 0.99]). Additional analyses identified potential reductions in acute kidney injury and respiratory failure; there was no evidence of increased risk of surgical site or other infections, or impaired wound healing.[44]

Surgical Site Infection

Chronic steroid therapy has been associated with an increased risk of wound infection, anastomotic leak, and poor wound healing, but not with single-dose or short-term treatment.[22] A meta-analysis evaluating a range of corticosteroids in oral surgery did not find any evidence of increased risk of infection in that setting.[28] A 2019 Cochrane systematic review and meta-analysis of 37 trials that enrolled 4,603 patients found no evidence that dexamethasone increased the risk of a postoperative wound infection (OR, 1.01 [95% CI, 0.80 to 1.27]) or wound healing (OR, 0.99 [95% CI, 0.28 to 3.43]).[45] A previous but more extensive systematic review reported equally reassuring findings.[46] Of interest, the DREAMS trial found that the incidence of anastomotic leak within 30 days of surgery was lower in the dexamethasone group (11 patients [1.6%]) when compared with the control group (21 patients [3.1%]) (RR, 0.53 [95% CI, 0.26 to 1.08]; $P = 0.08$).[22]

The most compelling data, however, come from the recently published PADDI trial.[43] Because of the ongoing concern that dexamethasone may increase the risk of surgical site infection, Corcoran *et al.* conducted a large, pragmatic, international, noninferiority trial that enrolled 8,725 patients undergoing noncardiac surgery of at least 2 h duration. The trial population included 1,149 (13%) patients with known diabetes. Patients were randomly assigned to

receive 8 mg IV dexamethasone or matched placebo after induction of general anesthesia, but before surgical incision. The primary outcome was surgical site infection within 30 days of surgery, and anastomotic leak and other sepsis outcomes were secondary endpoints. The prespecified noninferiority margin was 2.0%; this means that receiving dexamethasone would be considered "just as safe" as not receiving dexamethasone if the incidence of surgical site infections were not more than 2% higher in the dexamethasone group than that seen in the placebo group. The results were completely reassuring. Surgical site infection occurred in 8.1% of patients in the dexamethasone group and 9.1% of patients in the placebo group. The statistical test for noninferiority resulted in a P value less than 0.001, clearly demonstrating that dexamethasone did not meaningfully increasing the risk of surgical site infection. Results were consistent across prespecified subgroups, including in patients with diabetes (fig. 2).

Hyperglycemia and Diabetes Control

Dexamethasone is a glucocorticosteroid, so it is no surprise that it can increase blood glucose in surgical patients with impaired blood glucose tolerance or diabetes.[47,48] The 2014 consensus guidelines for management of postoperative nausea and vomiting state that dexamethasone is relatively contraindicated in labile diabetic patients[14]; however, more recent data provide reassurance.

The 2019 Cochrane review included eight trials enrolling 595 patients and found that dexamethasone led to a small increase in blood glucose within the first 12 h after surgery in patients *without* diabetes (mean difference, 0.7 mmol/l [95% CI, 0.3 to 1.2]).[45] This small increase in blood glucose is unlikely to be clinically important, but can be expected to increase the need for insulin therapy.[44] A randomized trial enrolling both nondiabetic patients and patients with type 2 diabetes randomly assigned to receive 8 mg IV dexamethasone or 4 mg ondansetron found that in diabetic patients, the mean maximum blood glucose was higher in the dexamethasone group when compared with ondansetron (14.0 ± 2.5 mM *vs.* 10.7 ± 2.4 mM; $P < 0.01$).[49]

A moderate degree of postoperative hyperglycemia may therefore occur with dexamethasone in patients with diabetes, and this may be influenced by the patient's preoperative glycemic control.[50] How often this occurs, how much more likely treatment with insulin is required, and whether it leads to adverse clinical outcomes has, until now, been largely unresolved. The PADDI trial collected detailed data concerning blood glucose and diabetes control.[43] Of the 1,149 (13%) patients with known diabetes, nearly all had type 2 diabetes and only 2.3% had insulin-dependent type 1 diabetes. Overall, the median difference in peak blood glucose in the first 48 h after surgery between the dexamethasone and placebo groups was 1.3 mmol/l (95% CI, 1.2 to 1.3). Insulin therapy was required in a small proportion of nondiabetic patients and was more common in the dexamethasone group (0.5% *vs.* 0.1%; RR, 4.74 [95% CI, 1.57 to 19.2]). Patients with diabetes were not at increased risk of surgical site infection if they received dexamethasone (fig. 2).

Perioperative Neurocognitive Disorders

Perioperative neurocognitive disorders encapsulate the cognitive impairment identified in the pre- or postoperative period,[51] including postoperative cognitive dysfunction and postoperative delirium. Although the underlying mechanisms are likely to be multifactorial, with both surgical and anesthetic triggers, systemic and neuroinflammation are likely to play a substantive role.[52] Thus, corticosteroids, at least theoretically, could mitigate the risk of perioperative neurocognitive disorders.

A meta-analysis of five randomized trials evaluating the effects of dexamethasone on postoperative cognitive dysfunction (three trials) and postoperative delirium (two trials) in adults found no significant difference between the dexamethasone group and the placebo group for both postoperative cognitive dysfunction (RR, 1.00 [95% CI, 0.51 to 1.96]; $P = 1.00$), and postoperative delirium (RR, 0.96 [95% CI, 0.68 to 1.35]; $P = 0.80$).[53] However, the quality of the evidence was considered low and the findings remain unreliable. Several clinical trials are currently underway that might resolve this uncertainty (*e.g.,* NCT02109081 and ACTRN12617001540303).

Optimal Dexamethasone Dose

Most studies evaluating dexamethasone in perioperative practice have used varied doses, often 4 or 5 mg, or 8 or 10 mg, largely because of ampoule or vial size/preparation available in the study setting(s). Unfortunately, there are very few head-to-head dose comparisons. The most recent systematic review examined perioperative dexamethasone use in 120 randomized trials, mainly administered intravenously at doses of 1.25 to 35 mg.[1] This review identified that moderate doses, most often 8 mg, seemed to be the optimal dose in perioperative practice. A dose of 8 to 10 mg dexamethasone had a significantly greater effect for reducing the incidence of postoperative nausea and vomiting than 1.25 to 5 mg dexamethasone. A meta-analysis of patients undergoing thyroidectomy found that dexamethasone at 8 to 10 mg had the greatest effect in reducing postoperative nausea and vomiting.[23] In the DREAMS trial, patients receiving the prophylactic single dose of 8 mg IV dexamethasone before surgery required fewer postoperative antiemetics for up to 72 h after surgery.[22] The PACMAN trial evaluated two doses (after surgery and on day 1) of 0.2 mg/kg IV dexamethasone, aiming for a reduction in serious complications or death.[44]

The optimal dose to achieve its maximal analgesic benefit is unclear. A recent randomized trial comparing two doses of IV dexamethasone (8 mg *vs.* 24 mg) in patients

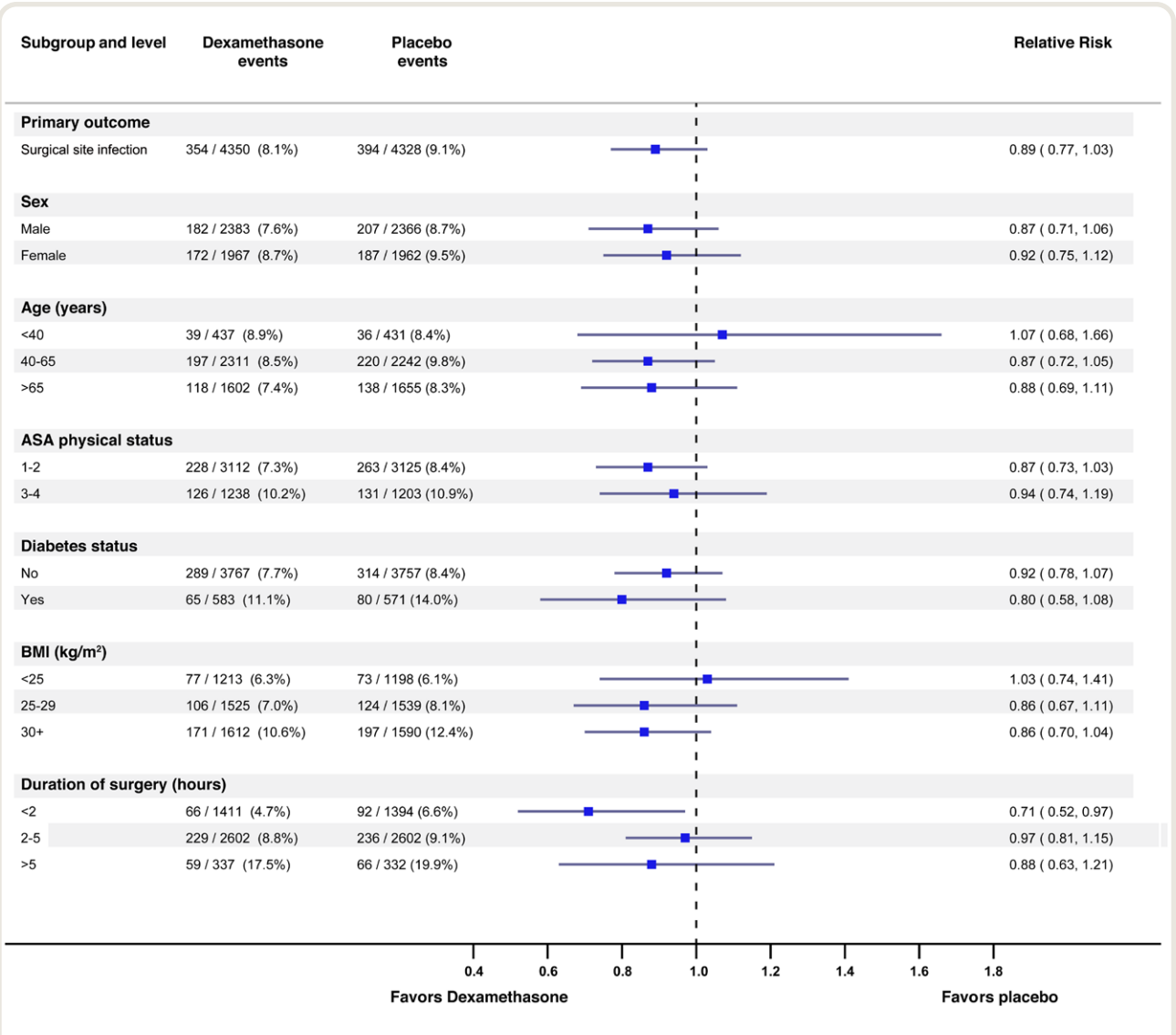

Fig. 2. The effect of 8 mg dexamethasone on the incidence of surgical site infection up to 30 days after surgery across subgroups. ASA, American Society of Anesthesiologists; BMI, body mass index.

undergoing mastectomy could not identify any measurable difference in pain scores, although the authors pointed out that most of their trial patients had modest pain and analgesic requirements.[54]

While 4 mg dexamethasone is effective in preventing and treating postoperative nausea and vomiting, slightly higher doses (8 to 10 mg) are needed to provide a better QoR, and possibly improved analgesia and less fatigue.[1,38] There is very little evidence that higher intraoperative doses (more than 10 mg) offer any additional benefit.

Conclusions

We recommend dexamethasone (4 to 8 mg) for the prophylaxis and treatment of postoperative nausea and vomiting; the higher dose provides an antiemetic benefit for up to 72 h.[22] A dose of 8 mg IV dexamethasone provides some analgesic benefit, particularly in orthopedic, oral, and ear, nose, and throat surgeries, and otherwise improves patient QoR after surgery. While dexamethasone increases blood glucose, particularly in patients with diabetes, the clinical significance of this is likely to be very small. The recent PADDI trial did not identify any increase in risk of surgical site infection when using dexamethasone (8 mg).[43] In fact, dexamethasone had little or no effect on any adverse events after surgery (RR, 0.77 [95% CI, 0.55 to 1.08]).[1] Dexamethasone is a cheap, safe, and effective drug in perioperative practice; more frequent use should be promoted.

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Competing Interests

The authors declare no competing interests.

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