Intravenous Dexamethasone as an Analgesic: A Literature Review

Sean G. Moore, MSN, CRNA

The management of pain in surgical patients has shifted in recent years from a technique grounded in opioid administration, to a multimodal method that uses the analgesic properties of many drugs to minimize required narcotics. Multimodal analgesia has demonstrated a benefit in patient outcomes following a surgical procedure. Also of consideration is the fact that multimodal analgesia allows for less opioid to be administered to achieve acceptable pain scores, in turn reducing a patient's exposure to a potentially addicting substance. Dexamethasone is a corticosteroid that has been widely used in the perioperative setting to prevent postoperative nausea and vomiting. The analgesic properties of dexamethasone have not been as widely acknowledged. A review of literature was conducted.

Multiple studies were found that demonstrated dexamethasone's ability to lower postoperative pain scores and reduce the amount of opioids required to achieve adequate pain scores. Single doses of dexamethasone have demonstrated safety with minimal side effects that would be expected from corticosteroid administration. Although an elevation in blood glucose levels is seen, this is likely of little clinical significance. No difference is seen in wound healing or rates of wound infection compared with control groups.

Keywords: Analgesic adjunct, dexamethasone, multimodal analgesia.

The management of acute surgical pain has shifted in recent years from a primarily narcotic-based technique to a system using drugs from multiple classifications known as multimodal analgesia. This technique, also known as balanced analgesia, strives to reduce the number of opioids required to reduce side effects as well as obtaining additional analgesic benefits. Pain is a prevalent reason for delayed recovery and discharge following ambulatory surgery and a common cause for unanticipated hospital admissions after what would otherwise be outpatient procedures.[1] Multimodal analgesia has demonstrated the ability to allow earlier oral intake, ambulation, and discharge in postoperative patients as well as quicker participation in rehabilitation activities such as physical therapy.[2] A reduction in the morbidity and mortality of surgical patients has also been demonstrated in patients who receive a balanced analgesic plan.[2]

Although the use of ketamine, gabapentin, acetaminophen, and nonsteroidal anti-inflammatory drugs has been well established in pain management,[3] the role and dosing of dexamethasone as an analgesic is relatively new. Dexamethasone is a synthetic corticosteroid, a fluorinated derivative of prednisolone, and an isomer of bethamasone.[4] Historically, dexamethasone has been used to treat a number of conditions, and its effectiveness has been well established in treating cerebral edema and the resultant increases in intracranial pressure due to tumors and metastatic lesions.[4] Also well established is dexamethasone's role as an antiemetic during the perioperative period.[4,5] Dexamethasone is believed to exhibit its postoperative antinausea and antivomiting effects by reducing surgery-induced inflammation because of its inhibition of prostaglandin synthesis.[4] The analgesic effects of dexamethasone come from inhibition of phospholipase that is necessary for the inflammatory chain reaction along both the cyclooxygenase and lipoxygenase pathways. The purpose of this review is to highlight recent studies that have established dexamethasone as a viable option for multimodal analgesia and to provide guidelines for dosing to achieve optimal effects of this medication.

Methods

An electronic search was performed using PubMed, MEDLINE, Cumulative Index to Nursing & Allied Health Literature, and Google Scholar. The search terms used were *intravenous dexamethasone, analgesia,* and *postoperative pain*. The search terms were limited to title and abstract only. The search was also limited to articles that have been published in the last 10 years.

This search yielded 67 articles, 7 of which were deemed appropriate for this review. Articles included examined the effects of intravenous (IV) dexamethasone on postoperative pain scores and analgesic requirements. Articles that investigated the effects of dexamethasone in combination with other nonnarcotic analgesics such as ketamine, nonsteroidal anti-inflammatory drugs, and gabapentin were excluded from this review. Articles that studied the effect of IV or perineural dexamethasone on extending the effects of regional anesthesia were also excluded, as the purpose of this review was to highlight dexamethasone's

analgesic properties, not its ability to extend the effects of other anesthetic and analgesic agents. Of the 7 articles that were deemed appropriate for this review, 2 were a meta-analysis, 4 were randomized controlled trials (RCTs), and 1 was a retrospective chart review.

Results

• ***Pain Scores.*** One of the most accepted ways of assessing a pharmacologic agent's analgesic effects is by examining patient-reported pain scores. Of the studies included in this review, 6 had a component of pain score assessment included in the study. De Oliveira et al[3] performed a meta-analysis of 24 RCTs that included 2,751 subjects. Inclusion into the meta-analysis required an RCT of a single perioperative IV dexamethasone injection and a placebo control group.[3] Trials were excluded if they contained more than 1 perioperative dose of dexamethasone, contained concurrent use of an alternative multimodal analgesic regimen, or if a direct comparison between dexamethasone and placebo groups could not be made. Early (0-4 hours) and late (24 hours) pain scores were examined, as well as pain at rest and with movement. Studies were also classified into 3 groups by the dose of dexamethasone they received; low (0.1 mg/kg or less), intermediate (0.11-0.2 mg/kg), and high (0.2 mg/kg). De Oliveira et al[3] determined that a statistically and clinically significant reduction in early (mean difference [MD] –0.32, 95% confidence interval [CI]) and late (MD –0.49, 95% CI) pain scores at rest, and early (MD –0.64, 95% CI) and late (MD –0.49, 95% CI) pain scores with movement are seen with intermediate and high dosing of dexamethasone.

Waldron et al[6] performed a meta-analysis of 45 RCTs that involved a total of 5,796 patients. Patients in the studies that were included were randomized into either a group receiving a perioperative dose of dexamethasone 1.25 to 20 mg, or a group receiving a placebo. Five studies that received multiple doses of dexamethasone were included. Of those studies, 21 had a comparator other than saline, including a 5-HT3 (serotonin) antagonist, droperidol, metoclopramide, midazolam, and haloperidol. Pain scores were examined using the Visual Analog Scale (VAS), and were reported at 2 hours and 24 hours postoperatively. Results of this meta-analysis demonstrated a statistically significant reduction (MD –0.49, 95% CI) in the VAS pain scores, but the clinical significance of this was debated because the difference between control and treatment groups was small.[6] Despite this questionable clinical significance, the study by Waldron et al is not discredited, because of the discovery of opioid-sparing properties of dexamethasone administration that will be covered later in this review.

Kardash et al[7] performed an RCT of 50 patients undergoing elective, unilateral, primary total hip arthroplasty, randomly assigning them to a control group or a treatment group. The treatment group received a single 40-mg dose of dexamethasone before surgery, and after they received an intrathecal dose of 15 mg of plain 0.5% bupivacaine, IV sedation with propofol followed. The results of this study did not indicate any improvement with pain at rest between the treatment group and the control group at any time.[7] However, pain with movement was significantly lower starting at the 12-hour mark in the group receiving dexamethasone, and persisting through the end of measurement, which occurred at the 48-hour mark.[7]

An RCT performed by Kim et al[8] examined the effects of dexamethasone on the inflammatory response and pain of women undergoing uterine artery embolization (UAE) for treatment of symptomatic fibroids. The main goal of the trial was to evaluate levels of inflammatory markers, including the white blood cell count, C-reactive protein (CRP), interleukin-6 (IL-6), and the stress hormone cortisol in patients undergoing UAE. Secondary goals of the study were to evaluate pain scores on an 11-point numeric rating scale (NRS). The 64 patients were randomly assigned to a treatment group receiving dexamethasone, 10 mg, or a placebo group receiving just saline. Results of the study demonstrated a significantly lower pain score on the NRS at 12 hours (MD –1.1, $P < .05$) and 24 hours (MD –1.4, $P < .05$) postoperatively in the group that received dexamethasone.[8] Of note, the patients who received dexamethasone demonstrated a significant inhibition of CRP, IL-6, and cortisol levels, indicating the drug's effectiveness at reducing inflammation and the stress response after UAE.[8]

Szucs et al[9] evaluated the analgesic effect of dexamethasone on patients undergoing operative fixation of a fractured femur neck. A relatively small sample of 37 patients was recruited and randomly assigned into a treatment group receiving dexamethasone, 0.1 mg/kg, or a control group receiving a placebo. The results of this study demonstrated a significant reduction of pain scores at rest (MD –3.1, $P = .0004$) 6 hours after surgery.[9]

A retrospective chart review was performed by Samona et al[10] that evaluated the effectiveness of dexamethasone at reducing pain scores in patients who underwent a single total knee arthroplasty. A sample of 102 patients were selected from a 6-month period and separated into a treatment group receiving 8 mg of dexamethasone or a control group that received none. Pain scores were evaluated using an NRS upon arrival to the postanesthesia care unit (PACU) and 12 hours, 24 hours, and 48 hours postoperatively. Results of this study differ from those previously presented in that NRS pain scores were only lower in the 24-hour postoperative period, but not on arrival to the PACU or at the 12- and 48-hour marks.[10]

• ***Opioid Consumption.*** Another measure of an effective analgesic adjunct in multimodal pain management is the effect it has on reducing the amount of opioids

required to achieve satisfactory pain levels. An estimated 6% of patients who are prescribed opioids after surgery will develop new persistent opioid use.[11] Among those who misuse prescription opioids, the National Institute on Drug Abuse[12] estimates that 4% to 6% will progress to heroin use. Of the studies included in this review, all examined dexamethasone's opioid-sparing effects postoperatively. Jokela et al[13] performed an RCT of 129 women undergoing laparoscopic hysterectomy. Subjects were randomized into 4 groups: a control group receiving a placebo and 3 treatment groups receiving an IV dose of 5 mg, 10 mg, or 15 mg of dexamethasone. The results of this study demonstrated that the opioid-sparing ability of dexamethasone was dose dependent.[13] Patients receiving 5 mg of dexamethasone saw no significant reduction in postoperative opioid consumption. In the first 2 hours following surgery, there was a significant ($P \leq .001$) reduction in the amount of oxycodone required by the 10-mg group (0.17 mg/kg) as well as the 15-mg group (0.17 mg/kg) compared with the control group (0.26 mg/kg). A significant ($P = .027$) reduction of total oxycodone dose required 24 hours postoperatively was also seen in the 15-mg group (0.34 mg/kg) compared with the control group (0.55 mg/kg).[13]

Both the meta-analyses performed by De Oliveira et al[3] and Waldron et al[6] examined the opioid-sparing effects of dexamethasone by looking at opioid consumption using IV morphine equivalents. De Oliveira et al[3] found no statistically significant reduction in IV morphine equivalents in subjects who received low-dose dexamethasone (< 0.1 mg/kg). A reduction of required IV morphine equivalent units was found to be statistically significant in the dexamethasone intermediate-dose group (95% CI = 0.11-0.2 mg/kg) and in the high-dose group (> 0.2 mg/kg). No reduction difference was noted *between* the intermediate- and high-dose group. Waldron et al[6] reported a statistically significant (95% CI) reduction in required IV morphine equivalents at 2 hours (–0.87 mg/kg) and 24 hours (–2.33 mg/kg) postoperatively in those receiving dexamethasone. Unfortunately, no dosing guidelines are outlined because the authors of the meta-analysis did not separate the dosages given into varying groups.

In the RCT performed by Szucs et al[9] of patients undergoing operative fixation of a fractured neck of the femur, 24-hour postoperative morphine consumption was significantly lower in the treatment group that received 0.1 mg/kg of IV dexamethasone. A retrospective chart review performed by Samona et al[10] demonstrated similar results with administration of 8 mg of IV dexamethasone resulting in lower oral opioid consumption over the 3-day admission following total knee arthroplasty. The RCTs performed by Kardash et al[7] and Kim et al[8] failed to find any difference in opioid consumption in treatment groups receiving dexamethasone vs control groups despite demonstrating a significant decrease in pain score in the group receiving dexamethasone.

• ***Adverse Effects.*** As with all medications administered, dexamethasone is not without potentially harmful adverse effects. Of the 7 studies included in this review, only 2 provided any analysis of potentially adverse effects. De Oliveira et al[5] examined differences in wound healing, wound infection rates, and blood glucose levels between the 3 treatment groups and control group. Ultimately there were no differences in these potential adverse reactions between the treatment groups and control group. The meta-analysis by Waldron et al[6] similarly assessed differences in wound healing, wound infection rates, and blood glucose levels. Although wound healing and wound infection rates yielded no difference, alteration in blood sugar levels postoperatively was found. Waldron et al[6] reported that no difference in blood glucose levels could be found 12 hours postoperatively, but 24 hours postoperatively a small increase in blood glucose levels was demonstrated. What effect, if any, this has on patient outcomes was not discussed.

Dexamethasone, being a corticosteroid, has the potential to increase a patient's blood glucose levels following administration. Of particular concern is the effect that dexamethasone administration will have on a diabetic patient's blood glucose levels. Hans et al[14] performed a study in which nondiabetic individuals and patients with type 2 diabetes were administered 10 mg of IV dexamethasone after the induction of anesthesia, and alterations in blood glucose levels were monitored. Reported results found that diabetic patients had a larger increase from baseline blood glucose levels than did nondiabetic patients and that the greatest increases were seen in patients with higher hemoglobin A1C levels and in those with an elevated body mass index.[14] The highest recorded blood glucose level was 232.2 mg/dL, and the authors argued that the elevations seen were of debatable clinical significance. Tien et al[15] performed a similar study examining the effect of 8 mg of IV dexamethasone on blood glucose levels of nondiabetic persons and patients with type 2 diabetes. Contrary to the study performed by Hans et al,[14] no difference was found in the percentage of elevation of blood glucose levels when they compared patients who have type 2 diabetes with nondiabetic individuals. Mixed results of reports are available on the role that dexamethasone has on blood glucose level alteration in diabetic patients, and if reported alterations are of any clinical significance, intuitively it makes sense to exercise caution when one is administering dexamethasone to patients with diabetes. Clinical judgment should be used on a patient-by-patient basis with emphasis placed on evaluation of the patient's preoperative control of blood glucose levels.

Another well-established concern with the administration of corticosteroids is the potential for wound infections and delayed healing. Three studies were found

Source	Study design	Sample size (N)	Dexamethasone dose	Results
De Oliveira et al,[3] 2011	Meta-analysis	2,751	Patients were separated into subgroups receiving dexamethasone at dosages < 0.1 mg/kg, 0.11-0.2 mg/kg, or > 0.2 mg/kg	Dexamethasone at dosages more than 0.1 mg/kg resulted in lower pain scores at 4 hours and 24 hours, and resulted in a reduction in the required morphine equivalent units required after surgery. No difference was seen in the intermediate-dose group vs the high-dose group.
Jokela et al,[13] 2009	Blinded RCT	129	Patients were randomly assigned to receive a placebo or dexamethasone, 5 mg, 10 mg, or 15 mg	Dexamethasone, 10 mg and 15 mg, results in decreased oxycodone consumption during the first 2 hours after surgery. Dexamethasone, 15 mg, reduces the amount of oxycodone required for the first 24 hours after laparoscopic hysterectomy
Kardash et al,[7] 2008	Double-blinded RCT	50	Patients received either a placebo or dexamethasone, 40 mg	Dexamethasone, 40 mg, has a prolonged suppressive effect on the inflammatory response and decreases dynamic pain 24 hours after total hip arthroplasty
Kim et al,[8] 2016	Blinded RCT	59	Patients received either a placebo or dexamethasone, 10 mg	Dexamethasone, 10 mg, resulted in lower pain scores at 12 and 24 hours following uterine artery embolization
Samona et al,[10] 2017	Retrospective chart review	102	Patients received either a placebo or dexamethasone, 8 mg	Dexamethasone, 8 mg, resulted in decreased pain scores 24 hours after total knee arthroplasty, as well as decreased oral narcotic consumption
Szucs et al,[9] 2016	Double-blinded RCT	30	Patients received either a placebo or dexamethasone, 0.1 mg/kg	Pain scores at rest were lower at 6 hours following operative fixation of a fractured femur neck, and cumulative morphine consumption was lower 24 hours after surgery
Waldron et al,[6] 2013	Meta-analysis	5,796	Patients were separated into subgroups receiving dexamethasone, either 4-5 mg or 8-10 mg	Pain scores were lower in patients who received dexamethasone, 8-10 mg, postoperatively at 2 and 24 hours, and a reduction of morphine equivalent units at 2 and 24 hours

Table 1. Study Design, Sample Size, Dexamethasone Dose, and Results for Studies Evaluating Analgesic Effects of Intravenous Dexamethasone
Abbreviation: RCT, randomized controlled trial.

Source	Adverse effect examined	Sample size (N)	Study design	Results
Bolac et al,[16] 2013	Surgical site infection, wound cellulitis, wound separation, fascial dehiscence	431	Retrospective chart review	No difference demonstrated in rates of surgical site infection, wound cellulitis, wound separation, or fascial dehiscence in patients who received dexamethasone compared with those who did not
De Oliveira et al,[3] 2011	Wound healing, wound infection rate, blood glucose levels	2,751	Meta-analysis	No difference found in wound healing, rates of wound infection, or postoperative glucose levels between the group receiving dexamethasone and the group that did not
Gali et al,[17] 2012	Wound infection rate	574	Retrospective chart review	No difference found in the rate of postoperative wound infection rates in patients who received dexamethasone compared with patents who did not
Hans et al,[14] 2006	Blood glucose levels in diabetic and nondiabetic patients	63	Prospective nonrandomized trial	Blood glucose levels were found to be marginally higher postoperatively in diabetic patients who received dexamethasone, although the clinical significance of this is debatable
Richardson et al,[18] 2016	Periprosthetic joint infection rate	6,294	Retrospective chart review	No difference was found in the rate of periprosthetic joint infections in patients who received an intraoperative dose of dexamethasone compared with those who did not
Tien et al,[15] 2016	Blood glucose levels in diabetic and nondiabetic patients	85	Randomized controlled trial	Dexamethasone increases postoperative blood glucose levels, but no difference was found in the level of increase between diabetic and nondiabetic patients
Waldron et al,[6] 2013	Wound healing, wound infection rates, and blood glucose levels	5,796	Meta-analysis	No difference was seen in wound healing or wound infection rates between the control and treatment groups. Blood glucose levels were found to be higher in the treatment group 24 hours postoperatively.

Table 2. Study Design, Sample Size, and Results of Studies Evaluating the Potential Adverse Effects of Dexamethasone Administration

in recent literature that demonstrated the safety of dexamethasone when given as a single IV dose to surgical patients. Bolac et al[16] performed a retrospective chart review of 431 patients who underwent laparotomy for treatment of endometrial cancer, of which 192 patients received a perioperative dose of IV dexamethasone ranging from 4 to 12 mg. Complications of surgical site infection, wound cellulitis, wound separation, and fascial dehiscence were searched for in the study. The resulting analysis found no difference in rates of wound complications in patients who received dexamethasone compared with those who did not.[16] Gali et al[17] performed a retrospective chart review of 574 patients who underwent urogynecologic procedures, of which 112 received a perioperative dose of IV dexamethasone ranging from 4 to 8 mg. The results of this study found no correlation between dexamethasone administration and postoperative wound infection. A retrospective chart review was also performed by Richardson et al[18] examining 6,294 patients who underwent total hip arthroplasty or total knee arthroplasty, of which 557 patients received perioperative dexamethasone ranging from 4 to 10 mg. The primary goal of this study was to examine possible differences in rates of periprosthetic joint infections between patients receiving dexamethasone and patients who did not receive a dose. Statistical analysis found no significant difference between the treatment group receiving dexamethasone and the control group receiving none.[18] Although delayed wound healing and increased risk of infections remains a concern for patients who receive an extended corticosteroid therapy regimen, single perioperative dosing of dexamethasone has been proved to have no significant effect on these postoperative complications.

Discussion

Multiple studies have demonstrated the ability of dexamethasone to reduce postoperative pain scores[3,6-10] and the amount of opioids required after a procedure.[3,6,9,10,13] (Tables 1 and 2) When dosing dexamethasone for postoperative nausea and vomiting prophylaxis, a dose of 4 to 5 mg seems to be generally accepted.[5] The dosing of dexamethasone required to provide analgesia seems to be a bit higher than what is given to prevent postoperative nausea. Analgesic properties seem to be observed when the administered dose falls in the 0.1 mg/kg range and higher. De Oliveira et al[3] most clearly established dosing guidelines, finding that intermediate dosing of 0.11 to 0.2 mg/kg provided significantly lower pain scores and opioid requirements, and that there was no statistical difference between the intermediate-dose group and the high-dose group that received greater than 0.2 mg/kg. Findings by Szucs et al[9] support this dosing as well, demonstrating benefits in patients receiving 0.1 mg/kg of IV dexamethasone. Three of the studies[8,10,13] demonstrated analgesic benefits providing a single dose ranging from 8 to 10 mg of dexamethasone. Although the dose administered was not weight based, one can assume that an appropriately sized adult received a dose equivalent to 0.1 mg/kg or higher.

Conclusion

As shifts in surgical pain management from an opioid-based technique to a multimodal technique continue to evolve, IV dexamethasone appears to be a viable adjunct. Although lower doses are effective at preventing postoperative nausea and vomiting, intermediate doses of dexamethasone of at least 0.1 mg/kg appear necessary to observe reduction of pain scores and opioid consumption. Single doses of dexamethasone have no effect on rates of surgical site infections or delayed wound healing. Elevations of blood glucose levels do occur following administration of dexamethasone, and whereas the clinical significance of this is debatable, caution should be exercised in patients with diabetes.

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AUTHOR

Sean G. Moore, MSN, CRNA, is a Certified Registered Nurse Anesthetist at ProMedica Toledo Hospital in Toledo, Ohio, and a DNP student at the University of Alabama in Tuscaloosa, Alabama. Email: sgmoore@crimson.ua.edu.

DISCLOSURES

The author has declared no financial relationships with any commercial entity related to the content of this article. The author did discuss off-label use within the article.