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Original Clinical Investigations

The Anti-inflammatory Effects of Perioperative Dexamethasone Administration and the Relationship to Pain: A Systematic Review and Meta-analysis

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Introduction

Post-surgical inflammation is a common adverse event that can have detrimental effects on the recovery phase for patients. Commonly associated with pain severity, inflammation can make the management of postoperative pain difficult. Of the multiple inflammatory molecules that can be found in an inflammatory response, interleukin 6 (IL-6) and C-reactive protein (CRP) are two of the most commonly assayed biomarkers of inflammation. Dexamethasone (DEX), with its anti-inflammatory properties, is thought to reduce IL-6 and CRP. It thus may reduce pain when administered perioperatively. In this review, we assessed the anti-inflammatory effects of DEX and the relationship of such effects in the management of postoperative pain.

Methods

We systematically searched PubMed, Embase, and Cochrane Library for randomized controlled trials using the following criteria: patients greater than or equal to eighteen years of age undergoing surgery. The intervention of interest is perioperative DEX administration and the control was normal saline or the absence of DEX administration. Primary outcomes included postoperative IL-6 and CRP levels, with a secondary outcome of postoperative pain scores. Utilizing the RevMan program, a meta-analysis was performed using a random effect model. Studies not able to be analyzed quantitatively were assessed through a narrative approach.

Results

We identified a total of nine studies with 1048 subjects which fulfilled inclusion criteria. Only three of the nine studies were able to be quantitatively analyzed. Our analysis of these studies favored DEX administration for the reduction of postoperative inflammation with regard to IL-6 (SMD = -1.88; 95% CI -2.28 - 1.48; $p < 0.01$; Figure 3a), and near significant difference with regard to CRP (SMD = -0.93; 95% CI -1.91 - 0.04; $p = 0.06$; Figure 3b). DEX administration was also shown to significantly reduce postoperative pain (SMD = -1.34; 95% CI -2.12 - -0.56; $p < 0.01$; Figure 3c). Qualitative analysis for eight of the nine studies favored the administration of DEX for the reduction of inflammation as well as postoperative pain. The total dosage of DEX administered ranged from 6.6 to 40 mg. Regarding complications after DEX administration, all nine studies reported no significant increase in the incidence of serious adverse effects, including hyperglycemia, surgical site infections, or impaired wound healing.

Conclusion

Dexamethasone is a commonly used medication for the management of postoperative nausea and vomiting. Additionally, administration of DEX perioperatively also appears to be efficacious in lowering inflammation and managing postoperative pain from various types of surgical procedures. Complications, including impaired wound healing, hyperglycemia, and surgical site infections, which have been reported in previous studies, have not been observed with significance with the administration of one or two doses of DEX as evidenced by the literature in this review. Further research may justify the

utilization of DEX as a means to reduce postoperative inflammation and subsequent pain.

INTRODUCTION

Post-surgical inflammation is a common adverse event that can have detrimental effects on the recovery phase for a patient. The acute inflammatory response to injury, whether local or systemic, involves multiple pathophysiological responses in the nervous, endocrine, and immune systems.[1] Being an evolutionary adaptation, the immune system helps to protect the host against invading pathogens through the secretion of proinflammatory cytokines, neutrophil activation, endothelial dysfunction, and tissue damage.[2] Of the multiple inflammatory molecules that can be found in such an inflammatory response, interleukin 6 (IL-6) and C-reactive protein (CRP) are two of the most commonly assayed biomarkers used to determine the severity of one's inflammation.[3]

Inflammation is thought to contribute to the sensation of pain, with some theories stating that the root of all pain is due to an inflammatory response.[4] In various pain syndromes such as arthritis, back pain, migraines, and fibromyalgia, cytokines have been shown to be involved in their pathophysiology, often being found in elevated quantities.[5-8] In literature, it has been purported that such inflammatory mediators can be affected by the perioperative administration of glucocorticoid steroids, as a result of the anti-inflammatory effects of such medications. One glucocorticoid steroid commonly used in the operative setting by anesthesiologists is dexamethasone (DEX), most often utilized for post-operative nausea and vomiting (PONV).[9] Through its anti-inflammatory properties, it is thought that the administration of DEX will not only reduce post-surgical inflammation, but also post-surgical pain.[9] Inflammation has been widely associated with pain, therefore, through the administration of an anti-inflammatory such as DEX, it can be expected that one's severity of pain may be decreased.[4,6] However, a systematic synthesis of studies that examine the relationship of inflammation through biomarkers and pain severity through pain scales in regards to DEX administration is lacking. Biomarker levels and pain scores help to provide estimates of the magnitude of the effect inflammation has on pain intensity. Bringing together and appraising research in the area would help to identify the relationship between DEX and inflammation, and the effect this relationship has on pain severity.

The aim of this systematic review was to therefore identify, synthesize, and critically appraise studies that have investigated the relationship between the biomarkers IL-6 and CRP, and visual analog scale (VAS) or numeric rating scale (NRS) pain scores, in the context of perioperative dexamethasone administration.

METHODS

We formulated our clinical research questions using the patient/population, intervention, comparison, and outcomes (PICO) framework (e.g. in patients undergoing surgical procedures, does the perioperative administration of dexamethasone affect post-operative inflammatory marker levels and post-operative pain scores?) and conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

A boolean search string was developed incorporating 'dexamethasone', 'interleukin 6', and 'C reactive protein' to perform a literature search in PubMed, Embase, and Cochrane Library (e.g. "post-operative pain OR surgical pain AND dexamethasone AND interleukin 6 OR IL-6 AND C reactive protein OR CRP"). Literature was managed using COVIDENCE (Cochrane Collaborative Group, London, UK) to screen studies for inclusion into this study, and EndNote for the compilation and organization of studies (Clarivate, Philadelphia, PA).

Studies comparing the effect of DEX on IL-6 and CRP as well as VAS or NRS pain scores in patients having undergone a surgical procedure were eligible. We included randomized controlled trials where DEX was the point of interest and the control groups were either given a placebo or did not receive DEX. Reviews, case reports, letters, conference abstracts, editorials, and notes were excluded from the study. Inclusion criteria for the studied population were adults greater than or equal to 18 years of age having undergone a surgical procedure. We excluded studies on patients not having undergone surgical procedures, and adolescents and children less than 18 years of age. The control was either no DEX administration or placebo such as normal saline. We included studies published in English, with no restrictions on the publication date.

There were 143 references imported for screening, with 58 duplicates removed. Two authors independently screened 85 titles and/or abstracts of records identified from database searches to identify those potentially meeting the inclusion criteria. We retrieved the full text of 15 potentially eligible studies and two authors independently reviewed them for eligibility. Six studies were excluded for reasons including unknown status of study, wrong comparator, or retracted study (Figure 1). Any disagreement over the eligibility of studies was to be resolved through discussion with a third reviewer, however there was no disagreement during the screening process.

The same two authors independently assessed the risk of bias in individual studies as per the Cochrane Handbook for Systematic Reviews of Interventions, through the use of the embedded risk of bias tool found within COVIDENCE (Cochrane Risk of Bias version 1). Study methods were categorized as "low risk", "high risk", or "unclear risk" of bias (Figure 2).

Data were extracted independently by the same two authors and discrepancies were resolved through discussion. We sought baseline and endpoint data for the primary outcome of IL-6 and CRP levels and the secondary outcome of pain score. Meta-analysis was performed for all outcomes using Review Manager 5 software. Due to the limited availability of data in some studies, a narrative approach was

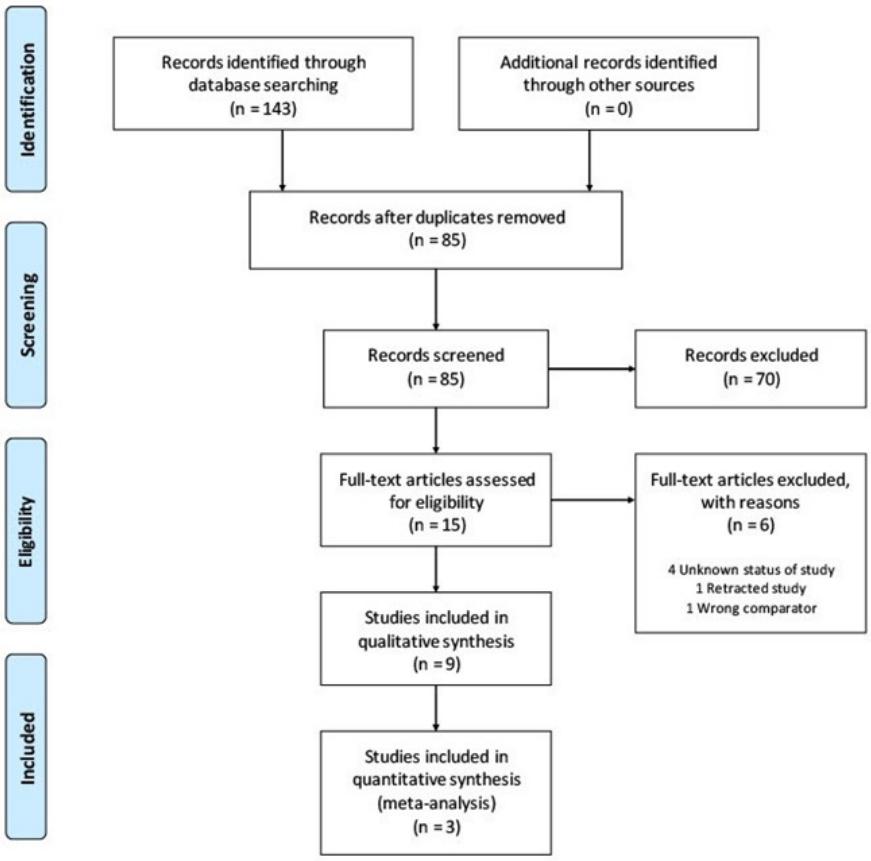

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram

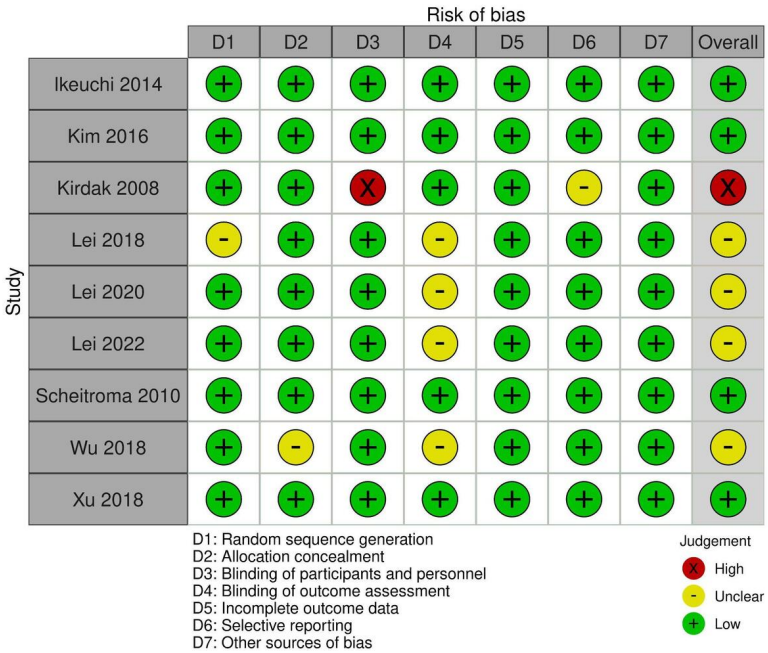

Figure 2. Cochrane Handbook for Systematic Reviews of Interventions Risk of Bias Plot

Figure 3a. Characteristics of Included Studies

First Author (Year)	Study Population	Dexamethasone Dose	Timing of Dexamethasone	Control
Ikeuchi (2014)[13]	40 patients undergoing total knee arthroplasty	6.6 mg (single dose, in combination with ropivacaine and isepamicin)	Intraoperative	Ropivacaine and isepamicin combination without dexamethasone
Kim (2016)[12]	59 patients undergoing uterine artery embolization	10 mg (single dose)	Preoperative	Saline equivalent
Kirdak (2008)[10]	30 patients undergoing colorectal surgery	8 mg (single dose)	Preoperative	Serum physiologic equivalent
Lei (2018)[17]	110 patients undergoing total hip arthroplasty	20 mg (two 10 mg doses)	Intraoperative and Postoperative	Saline equivalent
Lei (2020)[14]	165 patients undergoing total hip arthroplasty	Group B: 20 mg (single dose); Group C: 20 mg (two 10 mg doses)	Group B: Preoperative; Group C: Preoperative and Postoperative	Saline equivalent (Group A)
Lei (2022)[15]	192 patients undergoing total knee arthroplasty	Group B: 20 mg (single dose); Group C: 20 mg (two 10 mg doses)	Group B: Preoperative; Group C: Preoperative and Postoperative	Saline equivalent (Group A)
Schietroma (2010)[11]	82 patients undergoing laparoscopic floppy Nissen fundoplication	8 mg (single dose)	Preoperative	Saline equivalent
Wu (2018)[16]	150 patients undergoing total knee arthroplasty	Group B: 10 mg (single dose); Group C: 20 mg (two 10 mg doses)	Group B: Preoperative; Group C: Preoperative and Postoperative	Saline equivalent (Group A)
Xu (2018)[18]	182 patients undergoing total knee arthroplasty	Group B: 20 mg (single dose); Group C: 40 mg (one 20 mg dose and two 10 mg doses)	Group B: Preoperative; Group C: Preoperative and Postoperative	Saline equivalent (Group A)

used for studies that could not be quantitatively analyzed in the meta-analysis. For continuous variables, the standardized mean difference (SMD) was calculated with 95% confidence interval (CI). A random effects model was used in the meta-analysis. The overall effect was considered statistically significant when $p < 0.05$ (Figures 4a, 4b, and 4c).

RESULTS

STUDY CHARACTERISTICS

Nine studies were included with a total sample of 1006 participants undergoing various surgical procedures of various nature: six orthopedic, one gynecologic, and two gastrointestinal (Figure 1). All included studies were randomized controlled studies administering single or multiple doses of DEX perioperatively with comparison to a placebo (Figures 3a and 3b). Of the nine included studies, four administered a single dose of DEX either preoperatively or during the procedure. Three studies compared DEX to a saline placebo in varying dosages: two studies utilized 8 mg of DEX 60 to 90 minutes prior to surgery, and one study utilized 10 mg of DEX, all with comparison to a saline placebo.[11,12,16] The fourth study utilized an intraoperative injection consisting of 6.6 mg of DEX combined with ropivacaine and isepamicin, with comparison to an injection with only ropivacaine and isepamicin (Figure 3b).[10]

The remaining five studies administered multiple doses of DEX compared to both a single dose and a saline placebo. Two of these studies administered doses preoperatively and at 24 hours post-procedure with comparisons to two doses of saline, one dose of 20 mg DEX followed by saline, and two doses of 10 mg DEX.[14,15] Another study administered doses preoperatively and at six hours postoperatively with comparisons to two doses of saline, one dose of 10 mg DEX followed by saline, and two doses of 20 mg DEX.[17] One study administered a dose right after the administration of general anesthesia and once again postoperatively upon arrival to the inpatient unit, with comparison to two doses of saline and two 10 mg doses of DEX.[13] Lastly, a fifth study administered three doses of DEX: one dose preoperatively with the other two doses administered 24 hours and 48 hours postoperatively. Comparisons were made to three doses of saline, one dose of 20 mg DEX followed by 2 doses of saline, and one dose of 20 mg DEX followed by two doses of 10 mg of DEX (Figure 3b).[18]

Figure 3b. Timing of Drug Administration

		Timing of Drug Administration		
First Author (Year)	**Groups**	**Preoperative**	**Intraoperative**	**Postoperative**
Ikeuchi (2014)[10]			•	
Kim (2016)[11]		•		
Kirdak (2008)[12]		•		
Lei (2018)[13]			•	•
Lei (2020)[14]	A (control)	•		•
	B	•		
	C	•		•
Lei (2022)[15]	A (control)	•		•
	B	•		
	C	•		•
Schietroma (2010)[16]		•		
Wu (2018)[17]	A (control)	•		•
	B	•		
	C	•		•
Xu (2018)[18]	A (control)	•		•
	B	•		
	C	•		•

*Control groups not listed, except as noted otherwise

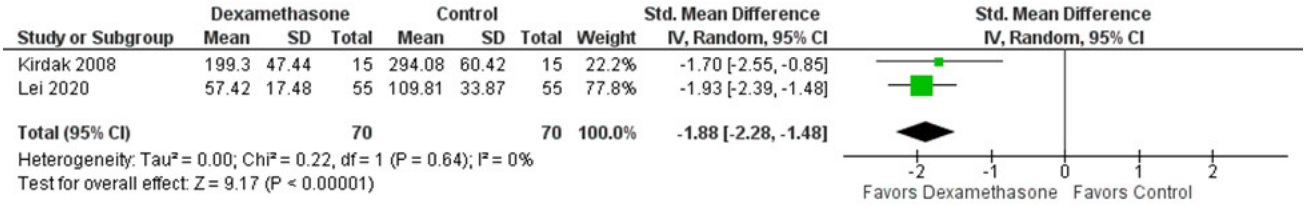

Figure 4a. Interleukin 6 (IL-6) Concentration Forest Plot

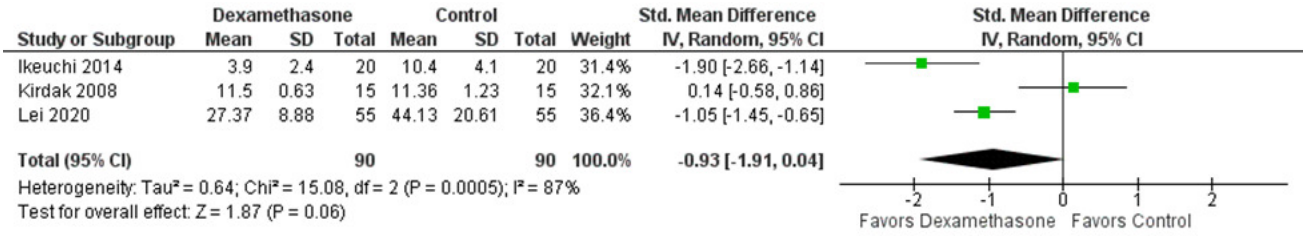

Figure 4b. C-Reactive Protein (CRP) Concentration Forest Plot

Of note, groups receiving only saline will be referred to as group A; groups receiving one dose of DEX and a placebo will be referred to as group B; groups receiving multiple doses of DEX will be referred to as group C.

IL-6

When measuring IL-6 levels, studies show that a single dose of DEX results in significantly lower levels of IL-6 on POD 1.[10,11] One study found that IL-6 had a significant increase in both groups, however the increase was significantly less in the DEX group.[16] A study by Kirdak et al. reported that while IL-6 increased significantly in both groups, there was no significant difference between them.[12]

Studies that administered multiple DEX doses found that IL-6 was significantly lower in groups B and C when compared to Group A on POD 1, 2 and 3 and significantly lower in group C than B on POD 2 and 3.[14,18] Another study found that IL-6 was significantly lower in group B when compared to group C and A on POD 1 and 2. Group C was signifi-

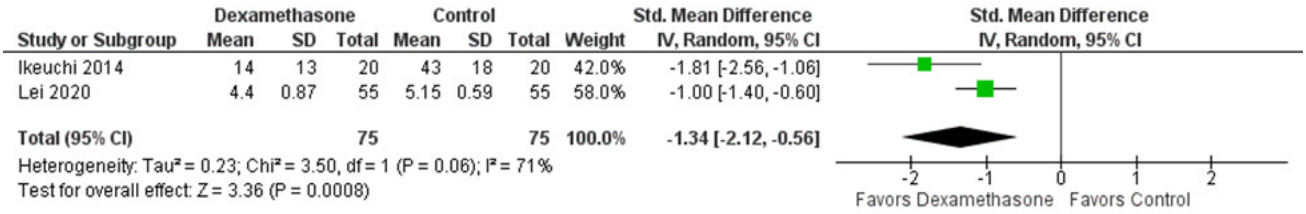

Figure 4c. Postoperative Pain Score Forest Plot

cantly lower than group A on POD 1 and 2. And Group C and B were significantly lower than group A on POD 3.[15] One study by Wu et al. also found that IL-6 levels in groups B and C peaked later (48 hours) than in group A (24 hours) and was significantly lower in group B and C when compared to A on POD 1, 2, and 3.[17] When comparing two doses of DEX to two doses of saline, it was found that IL-6 was significantly lower on POD 1, 2, and 3 in the group that received DEX.[13]

Statistical analysis of studies by Kirdak and Lei et al. favored DEX administration for the reduction of postoperative inflammation with regard to IL-6 (SMD = -1.88; 95% CI -2.28 - 1.48; $p < 0.01$; Figure 4a).[12,14]

CRP

Administering a single dose of DEX was found to significantly reduce CRP levels 12 hours after the surgery, on POD 1, and on POD 3.[10,11] Scheitroma et al. found that CRP significantly increased in both groups, however the increase was significantly higher in the placebo group than the DEX group.[16] Another study performed by Kirdak et al. found that there was no significant difference between CRP levels when comparing the DEX group to the placebo group.[12]

When multiple doses of DEX were administered, CRP levels were significantly lower in Group B and C compared to group A on POD 1, 2, 3, and significantly lower in group C than B on POD 1 as well as POD 2 and 3.[14,17,18] Lei et al. found that CRP levels were significantly lower in group B when compared to group C and A on POD 1 and 2. Group C was found to have significantly lower levels than group A on POD 1 and 2. CRP levels in Group C and B were significantly lower than group A on POD 3.[15] When comparing two doses of DEX to two doses of saline, there were similar significant results. CRP levels were lower in the DEX group on POD 1, 2, and 3 when compared to saline in another study by Lei et al.[13]

Analysis of three studies revealed a near significant difference between groups with respect to CRP levels (SMD = -0.93; 95% CI -1.91 - 0.04; $p = 0.06$; Figure 4b).[10,12,14]

POSTOPERATIVE PAIN

Regarding studies investigating the efficacy of a single preoperative dose of DEX, there were some contradictions with regard to pain rating on the respective pain scale employed. Two studies by Kim et al. and Ikeuchi et al. showed that patients reported significantly decreased pain 12 hours after the procedure, on postoperative day (POD) 1, and on POD 3.[10,11] Significantly decreased pain on POD 1 was also described by Scheitroma et al., with their study further suggesting that there was significantly decreased pain one week following DEX administration.[16] A study performed by Kirdak et al. found no significant difference with regard to pain scores between the DEX and placebo groups.[12]

Within the studies administering multiple doses of DEX, two studies conducted by Lei et al. found that groups B and C had significantly lower dynamic pain scores on POD 1, 2, and 3, and significantly lower pain scores at rest on POD 1 and 2.[14,15] It was also found that group C had a significantly lower dynamic pain score than group B on POD 1 and 3.[14] Similarly, group C was found to have significantly reduced pain when compared to B and A at POD 1, and B was found to have significantly reduced pain when compared to A on POD 1.[17] Another study by Xu et al. showed these exact findings to be true on POD 1, 2 and 3.[18] A third study by Lei et al. found that 2 doses of DEX significantly reduced dynamic pain only on POD 1 and there was no change in the severity of pain at rest when compared to placebo.[13]

Quantitative analysis of two studies favored the administration of DEX for the reduction of postoperative pain, with a significant difference seen between both groups (SMD = -1.34; 95% CI -2.12 - -0.56; $p < 0.01$; Figure 4c).[10,14]

COMPLICATIONS DUE TO DEXAMETHASONE ADMINISTRATION

While all studies documented complications, no complication significantly occurred in one group over the other. Common side effects accounted for in these studies include infection, impaired wound healing, gastric ulcers, ileus, pulmonary complications, and mortality.

DISCUSSION

The administration of dexamethasone perioperatively has been shown to be beneficial to with regard to various outcomes, such as a reduction in post-operative nausea, vomiting, and inflammation.[4,6,9]Most studies seem to have a consensus that overall pain, CRP, and IL-6 are decreased when a patient is administered DEX perioperatively when compared to placebo. The benefits of this adjunctive therapy seem to be transient, however, with most of the advantages coming within the first 3 days of administration. One study found that patients had decreased pain for as long as one week postoperatively.[16] Although transient, this decrease in pain and inflammation can prove para-

mount when discussing possible recovery, especially in orthopedics when movement is encouraged shortly after surgery.

There was one study that contradicted the others in which the authors found that there was no significant decrease in pain, CRP, or IL-6 with DEX administration.[12] While not discounting any findings, the small sample size (n=30) makes it difficult to determine if the null hypothesis was correctly accepted or if a type II error occurred.

The literature used for this study included not only those assessing the efficacy of a single dose of DEX, but also those assessing the efficacy of multiple doses as well. Comparing both of these approaches is important in guiding future clinical practice. Most of the data shows that multiple perioperative doses of DEX decrease pain to a greater extent than a single dose. Similar findings were also found with regard to both CRP and IL-6 levels. Both single and multiple-dose administration of DEX were found to decrease these inflammatory markers, with most studies finding that multiple doses decreased these markers to a greater extent than a single dose.[10-14,16-18] However, there was one study which demonstrated that a single dose of DEX was associated with a greater decrease in these inflammatory markers than multiple doses.[15] As a result, this ambiguity should be further explored in future studies to best determine how to implement perioperative DEX. Further research may justify the administration of dexamethasone in a perioperative setting as a means to reduce postoperative inflammation and pain, subsequently improving patient care as well as outcomes.

LIMITATIONS

A limitation of this study is that all included literature administered different doses and dosing schedules of DEX. This makes the comparison of one study to another very difficult, especially when considering a single dose of DEX versus multiple. Another limitation is that multiple surgical procedures were examined with varying levels of tissue trauma. Different procedures and techniques could cause variation with the effectiveness of DEX. A third limitation of this study is the small sample size of included studies. Extrapolating results from only nine studies brings into question the external validity of the findings.

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