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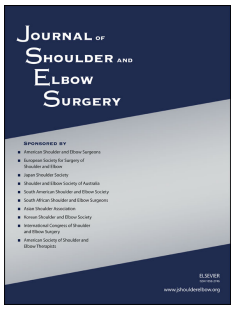

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Title

Dexamethasone decreases postoperative opioid and antiemetic use in shoulder arthroplasty patients: A prospective, randomized controlled trial

Authors

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Abstract

Background: Multimodal pain control can be beneficial in relieving postoperative pain and limiting narcotic use following orthopedic procedures. Additionally, with increasing interest in outpatient arthroplasty procedures, providers have interest in adequate early postoperative pain control and complications. The purpose of this study was to investigate the effect of dexamethasone on pain, postoperative nausea and vomiting and length of stay following total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA).

Methods: One-hundred and twelve patients undergoing TSA or RTSA by a single surgeon were assessed for inclusion in this investigation. We performed a prospective randomized, controlled trial to investigate the effect of 10mg of dexamethasone administered within 90 minutes of surgery. Primary outcome assessed was the average morphine equivalent use over the first 24 hours post-surgery. Secondary outcomes included postoperative visual analog scale (VAS) scores, anti-emetic use, postoperative nausea and vomiting and complications.

Results: A total of 75 patients were included in the final analysis with 32 patients (42.7%) randomized to the control group and 43 (57.3%) randomized to the dexamethasone group. Body mass index was significantly greater in the control group (33.8 vs 30.3, p=0.014), otherwise there were no significant demographic differences between groups. Average ondansetron use was significantly lower in the dexamethasone group compared to controls for the 0-4 hour interval (0.1 vs 0.9 mg, respectively, p=0.006) and was lower overall for the first 24 hours (0.3 vs 1.0 mg, p=0.025). Differences in VAS scores were significantly lower in the dexamethasone group at all time points ($p<0.05$ for all). The average VAS score over the 24-hour period for the dexamethasone group was also significantly lower than the controls (3 vs 6, $p<0.001$). Morphine equivalent use was significantly lower in the dexamethasone group compared to controls at 12-

16 hours (1.7 vs 4.0 mg, respectively, p=0.004) and at 16-20 hours (1.7 vs 3.4 mg, respectively, p=0.006). When averaged over the first 24 hours, morphine equivalent was also significantly lower in the dexamethasone group (16.1 vs 25.4 mg, p=0.007). There was no significant difference in glucose control or complications between groups.

Conclusion: Dexamethasone decreases opioid requirements in the first 24 hours following surgery, provides improved pain control, and decreases antiemetic use following shoulder arthroplasty. Dexamethasone is an important multimodal adjunct for controlling pain and postoperative nausea and vomiting following primary total shoulder arthroplasty.

Level of Evidence: Level I; Randomized Controlled Trial; Treatment Study

Keywords: Total shoulder arthroplasty, reverse total shoulder arthroplasty, pain, postoperative nausea and vomiting, multimodal pain control

The frequency of shoulder arthroplasty in the United States continues to increase, with a recent study reporting over 100,000 of these procedures performed yearly.[26] As the prevalence of both total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA) increase, so too does the importance of improving quality of healthcare and postoperative outcomes.

A recent analysis of over 10,000 patients undergoing inpatient procedures found that moderate to severe postoperative pain and severe postoperative nausea and vomiting (PONV) were associated with decreased patient satisfaction and increased length of stay (LOS).[17] Longer LOS is associated with increased cost of care, therefore there is a significant demand for interventions that reduce LOS.[8] Additionally, in an effort to improve patient satisfaction, the use of opioid pain medication in orthopedic procedures has been named as a leading contributor to

the American opioid epidemic.[24] Narcotic pain prescriptions have been identified as a major contributor to opioid addiction, resulting in a significant increase in opioid related deaths over the past few decades.[9,12] Therefore, reducing pain and PONV with multimodal regimens following shoulder arthroplasty could decrease both healthcare costs and the risk of opioid addiction following shoulder arthroplasty.

Dexamethasone is a potent, long-acting glucocorticoid that has been shown to target C-reactive protein and the proinflammatory interleukin 6, suppressing inflammation following orthopedic surgery.[27] Theoretically, downregulation of this inflammatory response could decrease postoperative pain. Furthermore, the drug has displayed potent, postoperative antiemetic effects.[15]

Multiple randomized controlled trials (RCTs) have reported decreased pain, PONV, LOS and opioid consumption in total hip arthroplasty patients treated with dexamethasone.[3,13,16] Additionally, a combination of dexamethasone and liposomal bupivacaine has been shown to decrease postoperative pain, PONV, opioid consumption and LOS in a small cohort of shoulder arthroplasty patients.[4,5,22] To our knowledge, the literature lacks a RCT evaluating the effects of dexamethasone alone following shoulder arthroplasty.

The purpose of this study was to perform a prospective, double blind, RCT to assess the impact of a one-time, preoperative, intravenous administration of dexamethasone on postoperative pain, nausea and vomiting, and opioid use in the first 24 hours following primary TSA or RTSA. We hypothesized that patients receiving dexamethasone would display decreased pain, opioid use, and PONV in the first 24 hours postoperatively compared to the control group.

Materials and Methods

Trial Design

Before beginning this prospective, double blind RCT, the study was approved by our institutional review board (IRB #11538). The hypothesis being tested was developed before data collection and the Consolidated Standard of Reporting Trials (CONSORT) guidelines were followed to perform the study.

Between August 2018 and March 2019, patients scheduled to undergo primary RTSA or TSA by one fellowship-trained shoulder surgeon (S.M.) were screened for study eligibility. Inclusion criteria were defined as patients over the age of 18 undergoing primary RTSA or TSA. Patients were excluded if they were undergoing revision surgery, indicated for surgery due to a proximal humerus fracture, or had a history of recent pregnancy, significant drug or alcohol abuse, steroid or immunosuppressive drug use within 6 months of surgery, and renal or hepatic failure.

Randomization and Blinding

Patients who decided to undergo RTSA or TSA were enrolled into the study by the principal investigator (S.M.). They were then randomly assigned to the dexamethasone or control group according to a randomization sequence, which used a 1:1 allocation ratio (Random.org, 2018). The anesthesia provider then administered intravenous dexamethasone if the patient was randomized into the treatment arm. The surgeon (S.M.) and patient were blinded to group assignments.

Interventions

Preoperatively, patients in both groups received one-time oral doses of acetaminophen 975 mg and pregabalin 100 mg. Patients in the dexamethasone group received an intravenous dose of 10 mg dexamethasone within 90 minutes of surgery. Both groups received an

intraoperative 62-mL local infiltration cocktail injected into multiple locations composed of the following medications: 300 mg (60 mL) 0.5% ropivacaine, 30 mg (1 mL) ketorolac and 10 mg (1 mL) epinephrine.

During the first 24 hours postoperatively, all patients received the following multimodal pain medication: acetaminophen 975 mg orally every 8 hours, oxycodone 5 mg orally as needed every 4 hours for moderate pain or 10 mg for severe pain, 7.5 mg meloxicam orally every 6 hours, gabapentin 100 mg orally every 12 hours and diazepam 5 mg orally as needed for muscle spasms. Furthermore, patients in both groups received additional opioid pain medication per the anesthesiologist's protocol to control breakthrough pain. Four-milligram intravenous doses of ondansetron were given postoperatively, every 4-6 hours as needed, to control postoperative nausea and vomiting (PONV). Prochlorperazine was used as a secondary antiemetic.

Outcomes

The primary outcome was mean morphine equivalent use over the first 24 hours postoperatively. Opioid usage was converted to milligram morphine equivalents (MME) and recorded in four-hour time intervals (www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf). Secondary outcomes included pain, the presence of PONV and anti-emetic use in the 24 hours following surgery as assessed by nurses in the recovery room and on the inpatient floor. Pain was assessed on a 10-point visual analog scale (VAS) by nursing staff. The highest pain score in each four-hour window following entrance to recovery was recorded. Patient-reported PONV and total antiemetic use were recorded in 4-hour time segments. Charts were reviewed at the time of study completion for complications including readmission, infection, reoperation, dislocation, deep

venous thrombosis, pulmonary embolism, pneumonia, and other postoperative occurrences. No changes to pre-specified primary and secondary outcomes were made during the study.

Following enrollment in the study, the following variables were extracted from the medical record: Age, sex, body mass index, surgery type, race/ethnicity, smoking status, diabetic status, and a glycated hemoglobin measurement taken less than 3 months before surgery.

Statistical and Power Analysis

An a-priori power analysis demonstrated a minimum sample size of 30 patients per group was required to detect a 30 percent between-group difference in the means of the primary outcome measure of average MME use over 24 hours at an alpha level of 0.05 and a power of 80%.

All variables were compared between control and experimental groups using univariate two-group t-tests or Wilcoxon rank-sum test for continuous variables and using chi-squared or Fisher's exact tests for categorical variables. Nonparametric tests are chosen when normality assumptions are violated and/or when effective sample sizes are <30. Glucose levels are compared between pre- and postop time points using the Wilcoxon signed-rank test due to a sample size of 15. All analyses are performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Demographics

Of the 112 patients evaluated for inclusion, 91 patients provided informed consent to participate in the study and were randomized, however 16 of these patients canceled their surgical procedure. A total of 75 patients were included in the final analysis, with thirty-two

patients (42.7%) randomized to the control group and 43 (57.3%) randomized to the dexamethasone group (Figure 1). There were no significant differences in the types of surgery performed between the two groups. Body mass index (BMI) was significantly greater in the control group (33.8 vs 30.3, p=0.014). There were no significant differences in the percentage of patients with diabetes, or in the preoperative glycated hemoglobin (HbA1c) value. Additionally, no significant differences were found in the percentage of preoperative opioid use or preoperative VAS score. Demographic variables are summarized in Table 1.

Postoperative Nausea and Vomiting

Differences in patient-reported PONV were evaluated at 4-hour intervals during the first 24 hours postoperatively and demonstrated no significant differences at all time points (Table 2). No patients reported PONV at the 12-16 and 20-24 hour intervals. Average ondansetron use was significantly lower in the dexamethasone group compared to controls for the 0-4 hour interval (0.1 vs 0.9 mg, respectively, p=0.006) and was lower overall for the first 24 hours (0.3 vs 1.0 mg, p=0.025, Figure 2).

Postoperative Pain

Differences in visual analog scale (VAS) scores were also assessed at 4-hour time intervals and scores were significantly lower in the dexamethasone group at all time points (Figure 3). The average VAS score over the 24-hour period for the dexamethasone group was also significantly lower than the controls (3 vs 6, p<0.001).

Morphine equivalent use was recorded for every 4-hour interval for the first 24 hours postoperatively and differences between the groups are shown in Figure 4. Morphine equivalent use was significantly lower in the dexamethasone group compared to controls at 12-16 hours (1.7

vs 4.0 mg, respectively, p=0.004) and at 16-20 hours (1.7 vs 3.4 mg, respectively, p=0.006). When averaged over the first 24 hours, morphine equivalent was also significantly lower in the dexamethasone group (16.1 vs 25.4 mg, p=0.007).

Preoperative Opioid Use

We performed a post-hoc analysis of patients who used opioid pain medication preoperatively. Among these patients, those who received dexamethasone (n=12) reported a significantly lower average VAS score (4 vs 6, p=0.010) and total morphine equivalent use (19.2 vs 35.9 mg, p=0.047) than those in the control group (n=9). However, average length of stay and total anti-emetic use were not significantly different.

Postoperative Course

Average length of stay was not significantly different in the dexamethasone group when compared to controls (1.1 vs 1.4 days, p=0.152). In diabetic patients, there were no significant differences in perioperative blood glucose between groups (Table 3). The average change in glucose across both groups was also calculated to be 14.1±28.9 mg/dL. The change from pre- to postoperative blood glucose was not statistically significant across the population (p=0.148).

Patients were followed for postoperative complications, with the shortest follow-up being 3 months and the longest 18 months. Two infections occurred, one in each group, and both were successfully treated with operative incision and drainage and antibiotics. There were also two reoperations, one in the control group for a subscapularis tear that required revision TSA and one in the dexamethasone group who required revision for instability.

Discussion

This study confirmed our hypothesis and demonstrated that use of preoperative dexamethasone in shoulder arthroplasty resulted in improved pain control with decreased morphine equivalent requirements and decreased antiemetic requirements. Additionally, this medication was demonstrated to be safe for use in the diabetic population with no significant changes in blood glucose. To our knowledge, this is the first randomized, controlled trial demonstrating the benefits of dexamethasone use in shoulder arthroplasty.

Dexamethasone is a corticosteroid that suppresses the inflammatory response to trauma, which makes it an attractive option for surgical patients. It inhibits transcription of genes for inflammatory mediators such as C-reactive protein and interleukin-6. This anti-inflammatory mechanism of action can decrease pain leading to decrease in opioid requirements in the postoperative period.[1,23] Many studies have examined the effectiveness of dexamethasone for perioperative pain control across various surgical specialties. In a meta-analysis of studies performed in various general and orthopedic surgeries, De Oliveira et al found that there was a dose dependent decrease in opioid requirements, with intermediate and high dose dexamethasone more effective than low dose. Additionally, they found the preoperative administration of dexamethasone provided a more consistent analgesic effect than intraoperative administration.[19] Fan et al performed systematic reviews on the effectiveness of dexamethasone on pain control following both total hip and total knee arthroplasty and found that dexamethasone significantly decreased VAS pain scores and opioid consumption following both procedures[10,11]. This is consistent with our findings demonstrating significantly lower morphine equivalent requirements when utilizing high dose dexamethasone. Orthopedic procedures are a major contributor to opioid prescriptions and with recent emphasis on controlling the opioid epidemic, dexamethasone may offer an additional avenue for decreasing narcotic use.[24] Although our study

was not powered to evaluate outcomes in chronic narcotic users, we demonstrated that patients with preoperative narcotic use had improved pain control with dexamethasone (Table 4). This indicates that dexamethasone can be a useful adjunct for patients with chronic pain.

Dexamethasone has also been shown in multiple studies to decrease postoperative nausea and vomiting.[15,25] The antiemetic mechanism of dexamethasone is less clear, but may be related to prostaglandin antagonism and endorphin production.[15] Dexamethasone is as effective as serotonin receptor antagonists, such as ondansetron, as a perioperative antiemetic.[25] This effect can last up to 24 hours after administration.[25] Bustos et al also investigated the utility of peri-operative dexamethasone for treating PONV following total joint arthroplasty and found that dexamethasone administration led to lower ondansetron use and length of stay following hip and knee replacement.[7] Our results also demonstrated the effectiveness of dexamethasone as an antiemetic, showing decreased ondansetron requirements in the first 0-4 hours after surgery, and lower requirements overall for the first 24 hours. This prolonged antiemetic effect is important as TSA is increasingly performed in an outpatient setting and prolonged nausea and vomiting can prevent same-day discharge.[2]

The safety and efficacy of perioperative dexamethasone in orthopedic procedures, particularly in total joint arthroplasty, is reported in the literature.[3,7,14] In a large randomized controlled trial, Backes et al demonstrated that preoperative dexamethasone decreased pain, nausea, and LOS in patients undergoing elective total hip or knee arthroplasty. Additionally, the benefits increased when a second dose was given at 24 hours postoperatively, with diabetic patients only experiencing a mild increase in blood glucose.[3] Others have found a reduction in the need for rescue antiemetics and reduced LOS, with no difference in infection rates at 30 or 90

days.[7] Our findings were similar, showing no difference in LOS but with significantly decreased morphine equivalent and antiemetic requirements.

There are few studies that have examined the use of dexamethasone in shoulder surgery. One study performed in shoulder arthroscopy and arthroplasty patients found that dexamethasone prolonged the effect of regional anesthetic blocks, and decreased opioid and antiemetic use when administered either perineurally or intravenously.[21] In a retrospective study, Routman et al examined interscalene nerve block compared to a combination of IV dexamethasone and local infiltration analgesia with marcaine and liposomal bupivacaine and found decreased pain and narcotic requirements with shorter LOS in the dexamethasone group.[22] Patients in the present investigation all received identical peri-operative analgesia with a combination of medications administered via local infiltration during the operation, limiting the variability seen with different types of regional nerve blockade. Our investigation found that dexamethasone was beneficial in decreasing morphine equivalent requirements over the first 24 hours postoperatively. With the current national opioid epidemic, orthopedic surgeons play a vital role in limiting narcotic prescriptions to prevent dependence and narcotic related morbidity.[28]

There are concerns regarding possible risks and adverse effects of dexamethasone use in the perioperative period. Some studies demonstrate a mild increase in postoperative blood glucose, which can be a concern in the diabetic population.[20,23] In total joint arthroplasty, Nurok et al found that dexamethasone did not increase the chance of postoperative blood glucose values over 200.[18] We did not exclude diabetic patients from our study and our results demonstrate that a single preoperative dose of dexamethasone is well tolerated in this population. All of our diabetic patients were well controlled as evidenced by their preoperative HbA1c, but poorly

controlled diabetics are typically excluded from elective procedures at our institution until they are optimized (HbA1c<8%). The risk of wound infection is another concern with dexamethasone use, however multiple studies have demonstrated that short-term or single-dose corticosteroids do not increase the risk of wound complications or infections.[7,14,20,23] Our results also demonstrated similar infection rates with only one infection in each group although the study was not powered to assess this outcome. Additionally, some studies have demonstrated that preoperative corticosteroid injections have a deleterious effect on microvascularization of the rotator cuff and subsequent healing.[6] However, there are no studies that report a negative impact of intravenous dexamethasone on subscapularis healing after shoulder arthroplasty.

Strengths of this study include the even distribution of RTSA and TSA surgeries, the inclusion of diabetic patients, and the inclusion of chronic narcotic users. The similarity in preoperative VAS scores demonstrates that preoperative pain and narcotic use were unlikely to be confounding factors. This study was not without limitations. The dropout rate was 18% (75 included out of 91 consented participants), however the most common reason was due to cancelled surgery. Visual analog scale scores are subjective and subject to bias. However, morphine equivalent use was also measured to provide a more objective measure of pain and demonstrated findings consistent with VAS scores. Data was only collected for the first 24 hours postoperatively so additional benefits or complications may have been missed. Intraoperative opiate dosing was recorded and included in the 0-4 hour time interval, however the decision for the type of medication and dose was made by the anesthesia team and was not controlled. Future studies can look at the utility of an additional postoperative dexamethasone dose, or the efficacy of using oral steroids compared to intravenous.

Conclusion

Dexamethasone provides improved pain control and decreases antiemetic use following shoulder arthroplasty. Opioid requirements in the first 24 hours following surgery were also decreased in the dexamethasone group. Dexamethasone is a viable option to use as a multimodal adjunct for controlling pain and postoperative nausea and vomiting following primary total shoulder arthroplasty.

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Figure Legends

Figure 1: Flow diagram demonstrating inclusion and final group allocation

Table 1: Comparison of type of surgery and demographic variables between experimental and control groups

Table 2: Comparison of postoperative nausea and vomiting at four hour intervals postoperatively between experimental and control groups.

Figure 2: Comparison of average ondansetron use every four hours between experimental (red) and control (blue) groups. * Indicates statistically significant difference between groups ($p<0.05$).

Figure 3: Average visual analog scale pain scores between dexamethasone (red) and control (blue) groups at four hour intervals. Difference is statistically significant at all times points ($p<0.05$). Abbreviations: VAS=Visual analog scale

Figure 4: Average morphine equivalent use at four hour intervals between control (blue) and dexamethasone (red) groups. Morphine equivalent dose in milligrams. * Denotes statistically significant difference ($p<0.05$).

Table 3: Average perioperative glucose levels for diabetic patients in both the control and dexamethasone groups.

Table 1. Demographics			
	Controls N = 32	**Dexamethasone N = 43**	**P-value**
Surgery			0.330
TSA	9 (28.1%)	8 (18.6%)	
RTSA	23 (71.9%)	35 (81.4%)	
Age, years Mean (SD)	66.6 (8.9)	67.1 (8.5)	0.835
Male	18 (56.3%)	21 (48.8%)	0.525
BMI, kg/m2 Mean (SD)	33.8 (6.1)	30.3 (4.7)	**0.014**
Diabetic	9 (28.1%)	8 (18.6%)	0.330
Preoperative HbA1c, % Mean, SD	6.7 (1.4)	7.3 (0.8)	0.306
Preoperative VAS Score	6.7 (2.9)	7.5 (2.6)	0.221

Preoperative Opioid Use	9 (28.1%)	12 (28.6%)	0.966

All values listed as N (Column percentage) unless otherwise specified. Bold values are statistically significant.

Abbreviations: TSA, total shoulder arthroplasty; RTSA, reverse total shoulder arthroplasty; BMI, body mass index; HbA1c, glycated hemoglobin; VAS (visual-analog score).

Table 1: Comparison of type of surgery and demographic variables between experimental and control groups

Table 2. PONV by Hours Postoperatively			
	Controls **N = 32**	**Dexamethasone** **N = 43**	**P-value**
0-4 hours	8 (25%)	6 (14.0%)	0.225
4-8 hours	5 (15.6%)	7 (16.3%)	0.939
8-12 hours	1 (3.1%)	1 (2.3%)	1.000
16-20 hours	1 (3.1%)	1 (2.3%)	1.000

Table 2: Comparison of post-operative nausea and vomiting at four hour intervals post-operatively between experimental and control groups.

Table 3. Perioperative Blood Glucose			
	Controls N = 4	**Dexamethasone N = 7**	**P-value**
Preoperative glucose (mg/dL)	139.3 (11.1)	165 (23.5)	0.072
Postoperative glucose	171.5 (36.7)	168.7 (14.9)	0.860

Table 3: Average perioperative glucose levels for diabetic patients in both the control and dexamethasone groups.

Table 4. Outcomes in patients with preoperative opioid use			
	Controls N = 9	**Dexamethasone N = 12**	**P-value**
Average VAS	6.2 (1.9)	4.2 (1.3)	**0.010**
Total MME	36 (25.0)	19 (9.6)	**0.047**
Total anti-emetic (mg)	0.9 (1.76)	0.0 (0)	0.094
LOS (days)	1.8 (1.3)	1.3 (0.9)	0.278

Table 4: Comparison of average VAS pain score, total MME and anti-emetic use, and length-of-stay in patients that used opiate pain medication preoperatively. Abbreviations: VAS: visual-analog scale; MME: milligram morphine equivalent; LOS: length of stay.

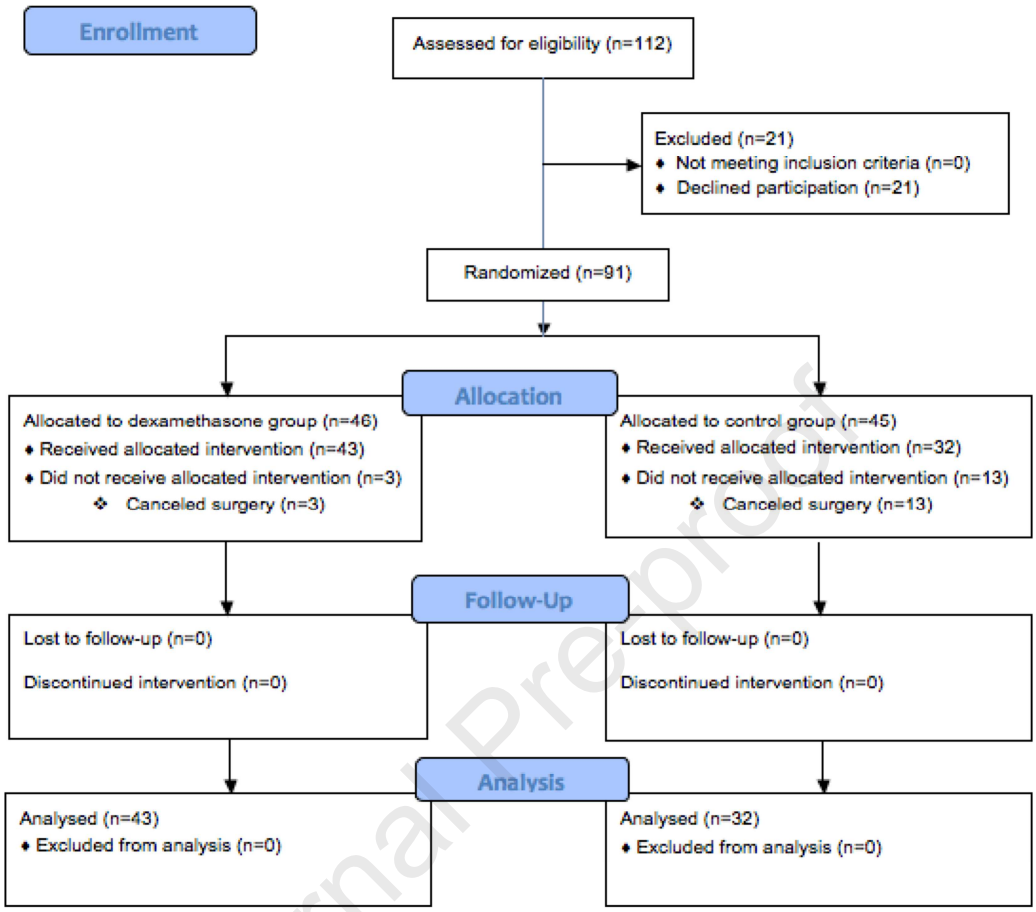

Figure 1: Flow diagram demonstrating inclusion and final group allocation.

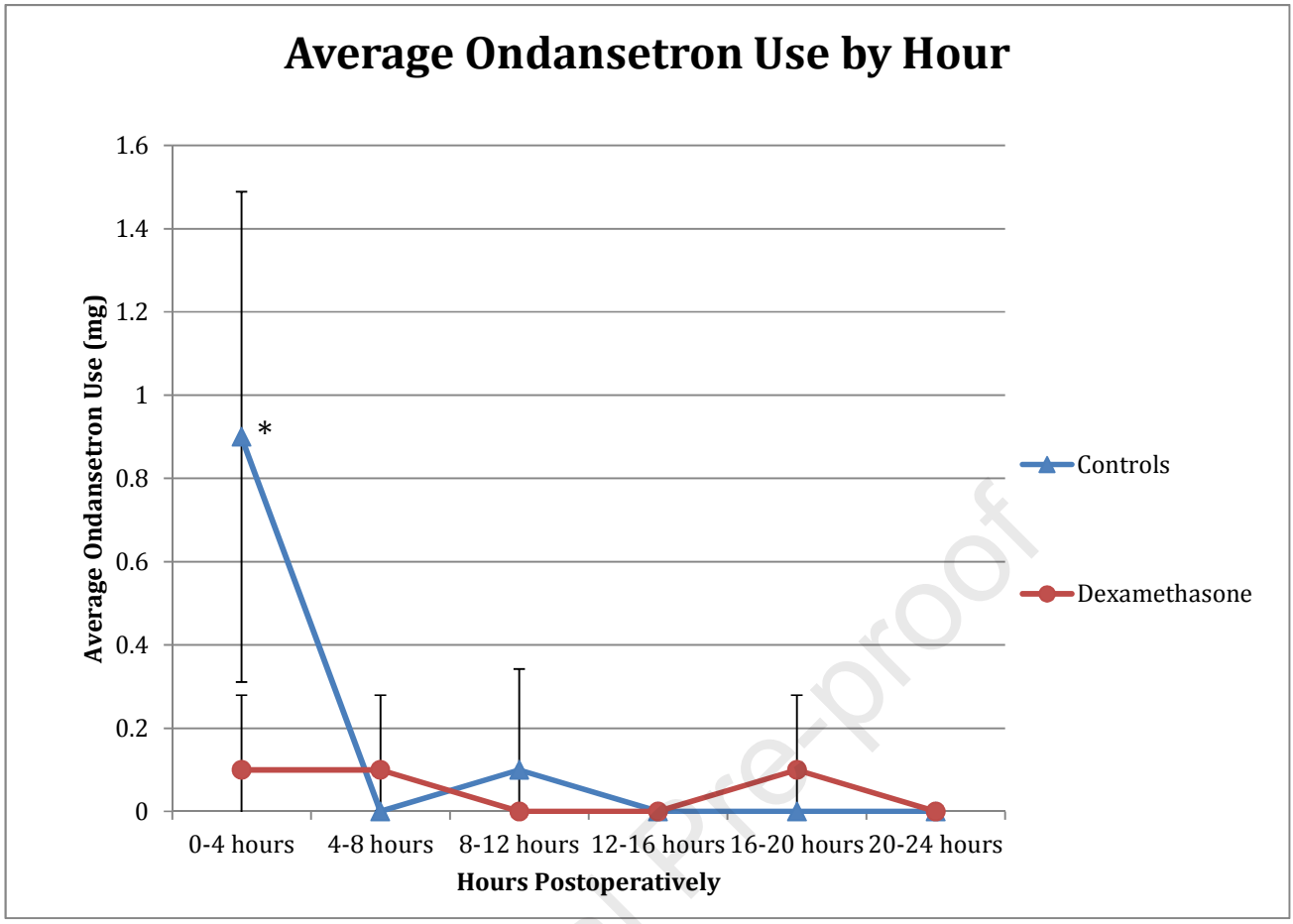

Figure 2: Comparison of average ondansetron use every four hours between experimental (red) and control (blue) groups. * Indicates statistically significant difference between groups ($p<0.05$).

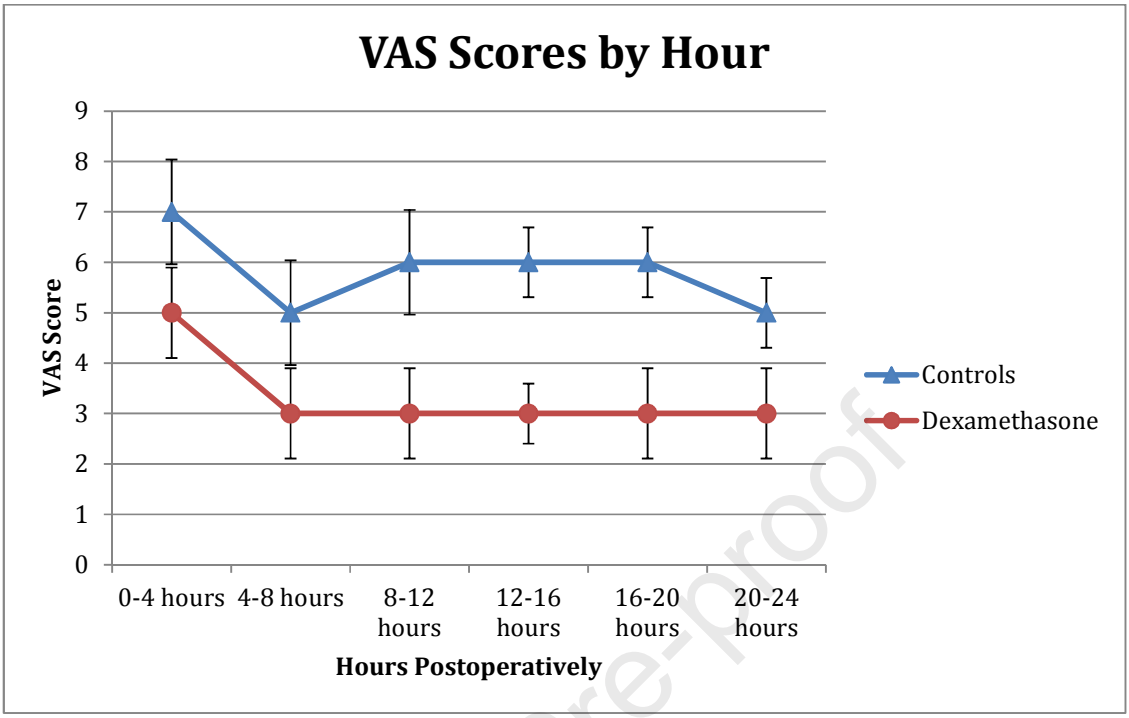

Figure 3: Average visual analog scale pain scores between dexamethasone (red) and control (blue) groups at four-hour intervals. Difference is statistically significant at all times points ($p<0.05$). Abbreviations: VAS=Visual analog scale

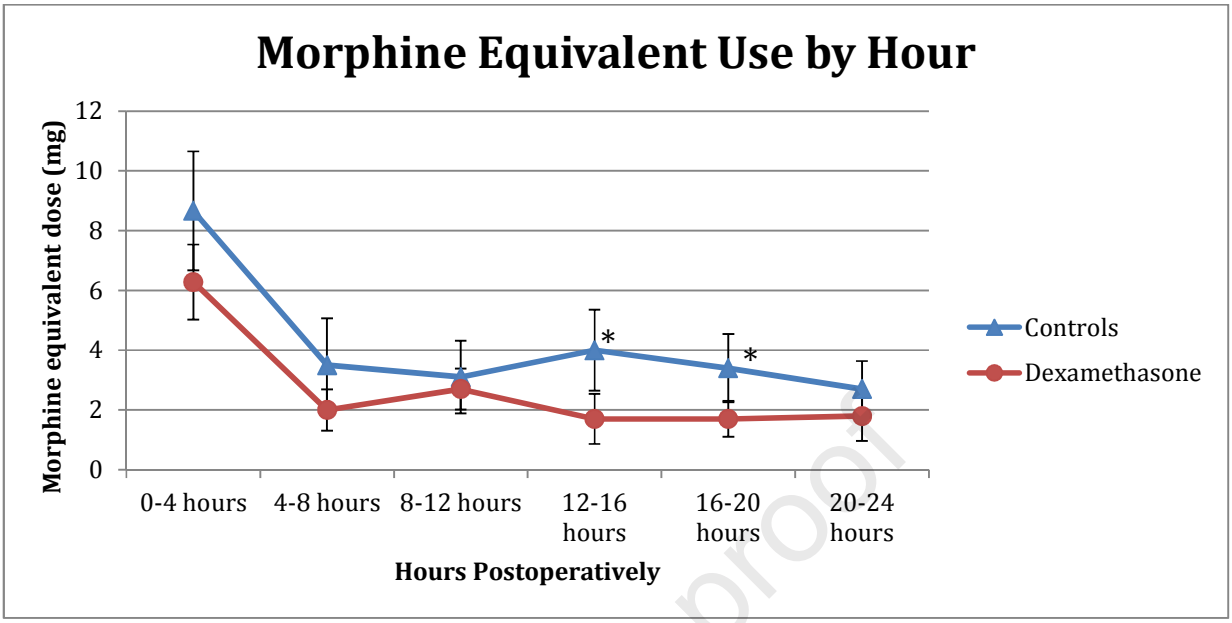

Figure 4: Average morphine equivalent use at four-hour intervals between control (blue) and dexamethasone (red) groups. Morphine equivalent dose in milligrams. * Denotes statistically significant difference ($p<0.05$).