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ORIGINAL ARTICLE

Comparing 8 mg versus 16 mg of dexamethasone as coadjuvant treatment for acute post-operative pain: A randomized controlled clinical trial

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Abstract

Background: *Glucocorticoids (IEA) have an analgesic effect by suppressing the release of inflammatory mediators that induce hyperalgesia, such as tumor necrosis factor-alpha, interleukin 8, and interleukin 6.* **Objectives:** *The objectives of this study were to compare two dosages of dexamethasone (DXM) (8 vs. 16 mg) as coadjuvant in the management of acute post-operative pain in patients undergoing ear, nose, and throat surgery.* **Materials and Methods:** *We included 80 patients in a double-blind clinical trial, divided into three groups that compared two different dosages of DXM with a control group that did not receive DXM, although all groups received intravenous (IV) analgesics. The post-operative pain report was assessed using a numeric rating scale, a post-operative pain visual analog scale (VAS), and recovery time 24-h after surgery. Descriptive statistics were used to apply the Chi-square test and ANOVA test for numerical variables.* **Results:** *Pain in Group 2 compared to Group 1 and Group 3 was less during recovery, after 1 h, and 24 h with $p < 0.05$ as with the post-operative pain VAS, $p < 0.05$. Opioid consumption was similar in the three groups.* **Conclusions:** *DXM 16 mg + Metamizole 1 g IV yields better analgesic effects compared to DXM 8 mg + metamizole 1 g in the immediate post-operative period and at 24 h.*

Key words: *Dexamethasone. Coadjuvant. Post-operative pain.*

Introduction

Surgical injury of the tissues causes neuroendocrine stress response and inflammation. This can be attenuated by regional or neuraxial anesthesia[1,2]. However, the inflammatory response acts systemically[3] and is responsible for serious complications that include prolonged fatigue[4], atrial fibrillation[5], delirium[6], and prolonged stay in intensive care unit[7]. It is also very likely that the inflammation grade contributes to the severity of acute post-operative pain[8].

Steroids have been used to reduce post-operative pain, as they inhibit phospholipase and thereby the products of cyclooxygenase and lipoxygenase pathways[9]. The expression of cytokine, bradykinin, and neuropeptide genes of injured nerve terminals is also inhibited[9-11], which may worsen pain.

In addition, they decrease the perioperative release of pro-inflammatory mediators and leukocyte adhesion molecules[10,11]. The effectiveness of steroidal anti-inflammatory drugs (SAID) in pain management has been

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assigned to the suppressed release of inflammatory mediators that induce hyperalgesia, such as tumor necrosis factor-alpha, interleukin 8, and interleukin 6[12], thereby decreasing inflammation-induced pain.

Hence, pre-operative or intraoperative administration of steroids may improve the quality of analgesia. Published studies have evaluated their effects for the prevention of post-operative pain, with additional short-term benefits, such as the prevention of post-operative nausea and vomiting even at low doses[13-17].

A meta-analysis conducted by De Oliveira et al.[16] reported that the administration of a simple dose of dexamethasone (DXM) in the post-operative period improves the analgesic effect.

Persistent incisional pain (for more than 3 months) is common, especially after surgeries, in which bleeding is > 500 ml, in bone deformities and/or wounds > 5 cm in the skin[16-18] which suggests that effective perioperative analgesia can help prevent the conversion of acute pain to chronic pain. However, the potential effect of steroids on persistent incisional pain remains unknown[19,20].

Poor management of acute post-operative pain is not free from risks or complications such as alveolar hypoventilation responsible for atelectasis, ileus, post-operative nausea, and vomiting, among others. Moreover, the likelihood of post-operative pain become chronic pain remains latent[21].

There are several analgesic schemes for post-operative pain treatment. Most schemes described for a successful management are based on the combination of two or more drugs[22]. The apparent interaction between the mechanisms of the action of non-SAIDs (NSAIDs) and SAIDs suggests that combined therapies can be beneficial in inflammation and pain control, if a single dose is administered to avoid the onset and progression of the inflammation cascade through phospholipase pathway[10,22-23]. Conversely, the potential risk of administering steroids in the perioperative period is far from trivial, as infection of the surgical site remains a frequent and serious complication[24].

DXM is one of the steroids that has been established with an analgesic effect, deemed one of the most versatile SAIDs, being also used in the prophylaxis and treatment of nausea and vomiting, during the post-operative period[25-28] as well as secondary to chemotherapy. Furthermore, it has been successfully used in the reduction of edema and post-operative stridor[29,30].

Ear, nose, and throat (ENT) surgeries carry a high risk of post-operative nausea and vomiting associated with significant pain after surgery[31-33]. Three different types of pain have been identified: incisional, visceral, and shoulder pain. Local infiltration anesthesia (Ropivacaine, Lidocaine, or Bupivacaine), together with the use of steroids, has been effective in controlling pain after this type of surgical intervention[34,35].

One of the proposed drugs for the administration of multimodal analgesia is DXM. However, more studies are necessary to establish the risk-benefit ratio for its use[36].

Several studies have recommended a dose of 5-8 mg IV of DXM mainly to reduce post-operative nausea and vomiting. However, as an analgesic in combination with drugs belonging to the NSAID group, its risk benefit in reducing pain and convalescence of patients after undergoing ENT surgery has not yet been assessed.

As DXM is widely used in the transoperative period of patients, this study aims to assess whether 16 mg of DXM is a better analgesic dosage than 8 mg for acute post-operative pain in patients undergoing ENT surgery.

Materials and methods

Study framework and participants

The study was approved by the Ethics and Research Committees of Hospital de Especialidades del Centro Medico Nacional Siglo XXI del Instituto Mexicano del Seguro Social with Registration Number 2014-3601-81 and Dr. Dulce María Rascón Martínez was assigned as principal investigator. Subjects were recruited at the same hospital and were invited to participate in the research during the pre-anesthetic visit the day before the surgery. Patients were scheduled for surgery corresponding to the otorhinolaryngology subspecialty under general anesthesia. Patients classified as the American Society of Anesthesiologists (ASA) I, II, and III were included, according to the standards and guidelines of the ASA. Exclusion criteria included patients with contraindications and/or allergic to DXM or metamizole, diabetic patients (glucocorticoids trigger glycemic decontrol in these patients), and surgeries >6 h (as the antiemetic effect of DXM will not be at its peak), in addition to patients that due to the complexity of the surgery or decision of the anesthesiologist in charge of the procedure, were admitted to different protocols than the one proposed for acute post-operative pain management.

Study design and procedures

We conducted a prospective, longitudinal, controlled, double-blind, and randomized clinical trial. Assignment

to each group was based on a random number table. An independent researcher received a numbered and sealed envelope that informed the name of the drug to be prepared. The medication was administered 30 min before the surgical incision as follows: Group 1; 8 mg of DXM were given in 10 ml saline and the subsequent administration of metamizole established at 15 mg/kg and Group 2; DXM 16 mg plus metamizole under the same administration method as Group 1. To patients in Group 3, they were administered a placebo that consisted only of 10 ml of 0.9% saline plus the subsequent administration of metamizole as in the other groups.

As a safety measure, baseline glucose levels were recorded between the groups by monitoring arterial blood gas (ABG) 2 h after the end of the surgical procedure. Each group was evaluated for pain, anxiolytic dosages, as well as opioid consumption during surgery.

Statistical analysis

Subjects who reported pain improvement after the use of DXM were the main variable used to calculate the sample size. A meta-analysis was used as reference, in which a difference in medians (MD) of −0.49.38 was reported. Thus, by assuming α level of 0.05 and a β power of 80% for a two-tailed test, at least 31 patients were required per treatment group. We chose to add nine (10%) patients to the sample, considering that some of them could not finish the study.

The description of demographic and clinical variables was performed using frequencies and percentages for categorical variables and with means and standard deviations (±) for continuous variables.

Results

Ultimately, 102 patients were included in the trial. Twenty-two patients were excluded for the following reasons: five patients withdrew their consent; in nine cases, surgery was suspended by the service due to causes unrelated to the study; in six cases, an analgesic scheme different from the one proposed in the study was used; and finally, two patients showed increased blood sugar levels before surgery. In all surgeries, patients underwent inpatient care (no ambulatory surgery).

The average age was 52 ± 1.74 years of age, with p = 0.137. Of the total sample analyzed, 62.5% (n = 50) corresponded to the female gender and 37.5% (n = 30) to the male gender. About 98.8% of patients (n = 79) were classified as ASA 2 and 1.2% (n = 1) as ASA 3. All patients underwent ENT surgery, the distribution of surgeries is shown in Fig. 1.

Pain assessment

To perform the statistical analysis of pain behavior, normality tests were conducted initially to determine if it was possible to analyze the groups by means of an ANOVA test, the variables that had a normal distribution obtained p > 0.05.

Numeric rating scale measurements were made on admission to the post-anesthesia care unit (PACU) and 24 h after discharge from the operating theater. Detailed data distribution between the groups is shown in table 1, which contains the pain report, according to the self-reported visual analog scale (VAS) of post-operative pain applied at 24 h (Table 1).

The differences between the groups are shown in Figs. 2-5.

Regarding opioid consumption used during the surgical procedure, 302.00 ± 42 mcg of fentanyl were used for Group 1; 311.11 ± 64 mcg were used for Group 2; and 317.86 ± 43 mcg for Group 3. With an average consumption of 310.66 ± 50 mg for all groups, no statistically significant differences were found for this variable, with p = 0.530.

Likewise, we quantified the amount of anxiolytics used. The need for administration of anxiolytics during the anesthetic procedure was only necessary in approximately 30% of participants of each group: seven patients in Groups 1 and 2 and eight patients in the control group. The average administration of anxiolytics for all groups resulted in 0.30 mg ± 0.5 (p = 0.762).

Glycemia

In an additional analysis, a glycemic index measurement was carried out, considering the baseline values obtained by the pre-operative blood chemistry and ABG control approximately 2 h after the end of the surgical procedure. This control was performed only in half of the patients (15 patients in Group 1, 11 patients in Group 2, and 13 patients in the control group). Because no clinically relevant increases in the glycemic index of the first 40 cases were observed during the study, and as the sampling method for blood sugar level measurement is deemed invasive, the researchers decided to suspend these measurements. The mean pre-operative glycemic index between the groups was 106.62 ± 25 (p = 0.224) mg/dl and the post-operative mean was

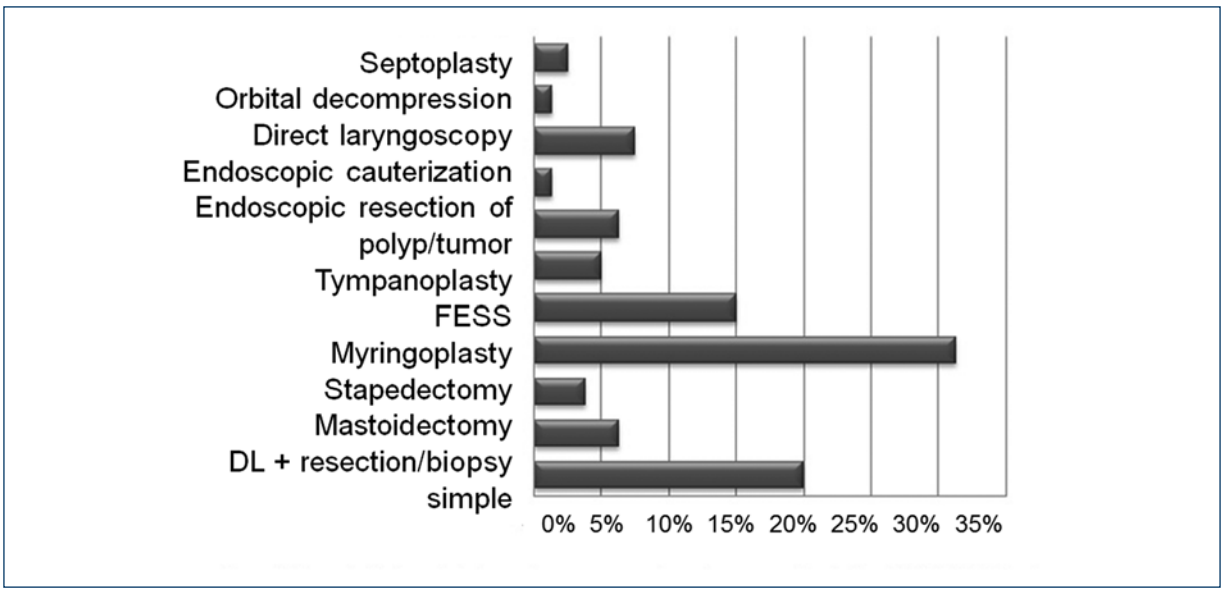

Figure 1. Surgical procedures to which study groups were subjected.
FESS: functional endoscopic sinus surgery; DL: direct laryngoscopy. Chi-square analysis.

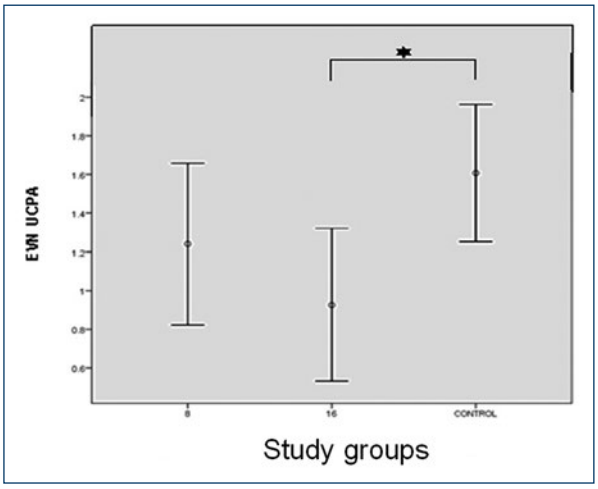

Figure 2. Assessment with numeric rating scale on admission to the post-anesthesia care unit using ANOVA. $p < 0.05$, analysis between groups on *post hoc* tests: Tukey.

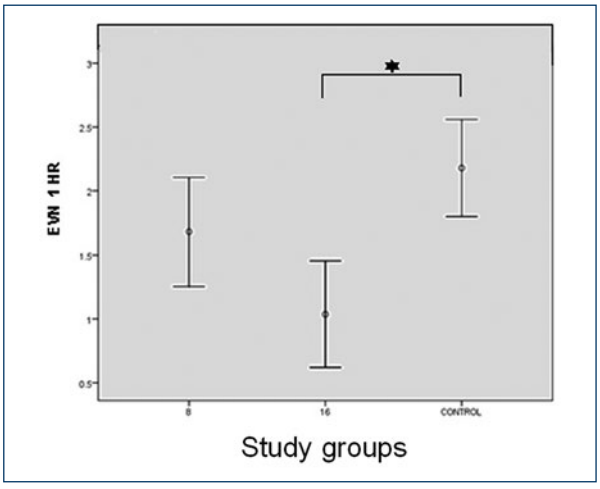

Figure 3. Pain assessment with verbal numeric scale 1 h after surgery using one-way ANOVA – $p < 0.05$, analysis between groups on *post hoc* tests: Tukey.

116.08 ± 31 mg/dl with no statistically significant differences ($p = 0.999$).

Discussion

In our study, the use of DXM during the transoperative period proved to be beneficial for pain control, due to the behavior of the pain reports of post-operative patients from ENT surgery.

Pain scores in this type of surgery were reported as mild or nonexistent, as only Grades 1-3 were reported and patients did not require rescue analgesics in the post-operative period, which is reflected in the same self-reported VAS of post-operative pain. The patients who were administered DXM mostly reported a VAS score < 2. Therefore, we can infer that the surgeries were not associated with greater intensity pain.

Table 1. Pain report of the analyzed groups

Numeric rating scale	Dexamethasone group 8 mg	Dexamethasone group 16 mg	Control group	p value
PACU ($\bar{X}$ ±SD)	1.24±1.01	0.93±0.99	1.61±0.91	0.040
CI 95%	0.82-1.66	0.53-1.32	1.25-1.96	
1 H ($\bar{X}$ ±SD)	1.68±1.03	1.04±1.05	2.18±0.98	0.000
CI 95%	1.26-2.10	0.62-1.45	1.80-2.56	
24 H ($\bar{X}$ ±SD)	1.32±0.96	1.0-1.24	2.36±1.19	0.000
CI 95%	1.12-1.92	0.51-1.49	1.89-2.82	
VAS				
24 H ($\bar{X}$ ±SD)	1.56±0.71	1.41±0.57	2.29±0.85	0.000
CI 95%	1.27-1.85	1.18-1.63	1.95-2.62	

SD: standard deviation; CI: confident interval; PACU: post-anesthesia care unit; VAS: visual analog scale.

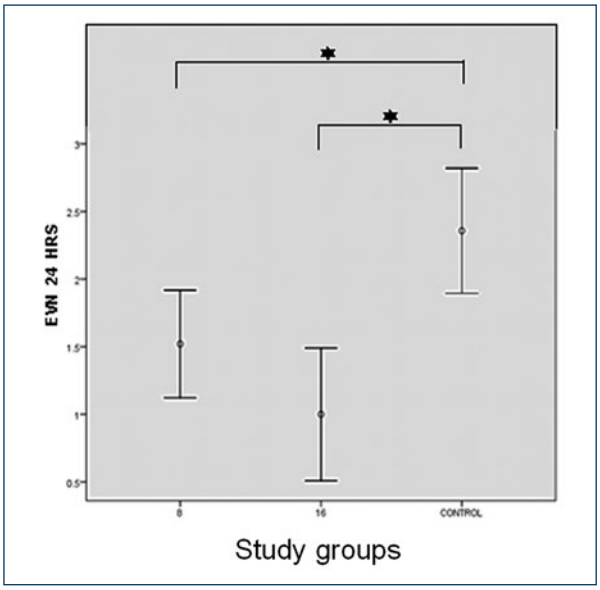

Figure 4. Pain assessment with verbal numeric scale 24 h after surgery using one-way ANOVA – $p < 0.05$, analysis between groups on *post hoc* tests: Tukey.

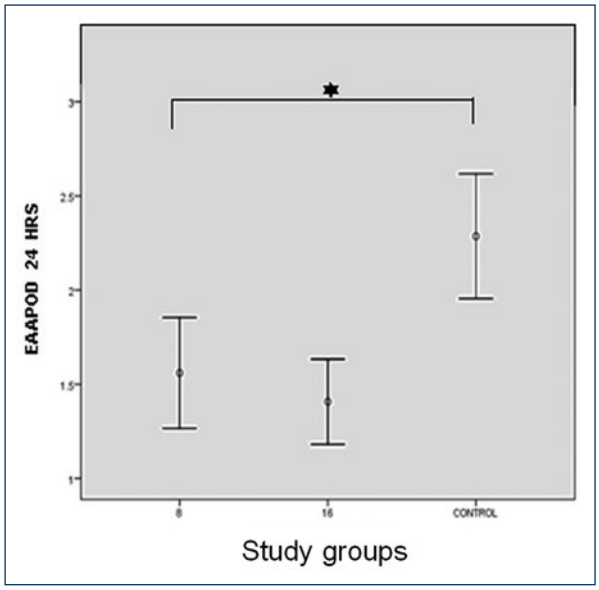

Figure 5. Assessment with the self-reported visual analog scale of post-operative pain 24 h after surgery using one-way ANOVA – $p < 0.05$, analysis between groups on *post hoc* tests: Tukey.

The pain during the PACU stay was considerably lower as well as at discharge and at the first 24 h after surgery. The effect of the opioid used during the surgery was discarded, as no significant differences were observed in its consumption between the groups. The graphs show that these pain reports have a better performance when a dose of 16 mg DXM was used in the measurements. A potential explanation is that the inflammatory response to surgical injury of the tissues is largely responsible for the pain intensity in the post-operative period[4] and the glucocorticoid inhibits the phospholipase peripherally, affecting cyclooxygenase and lipoxygenase pathways[16].

In our study, we decided to perform a blood glucose measurement 2 h after the surgical procedure, without detecting any significant increased levels. It is worth

considering that after the administration of DXM, maximum blood glucose levels occur between 8 and 10 h, so measurement times could explain this result. However, we think that the inclusion of non-diabetic patients and the use of a single dose of the steroid have no clinically relevant alterations in the glycemic index. Due to the study design, this finding cannot be asserted and more in-depth studies will be required for better methodological design of this aspect and with measurements up to 12 h after the administration of DXM to detect maximum glycemic values.

Multiple studies suggest that intermediate doses of corticosteroids, such as DXM, seem to be the safest and most effective option of multimodal analgesia. It also shows that analgesia is greater when steroids are administered preoperatively (at least 1 h before surgery) or during the induction of anesthesia[6,10,15,22]. Hence, post-operative pain treatment with a multimodal technique that includes DXM as a coadjuvant, decreases pain scores and the use of rescue analgesia during the first 24 h of the immediate post-operative period[10,15,22,37]. The results of our study were no exception.

Systematic reviews have been performed where it can be concluded that a single perioperative intravenous (IV) dose of DXM had small but statistically significant analgesic benefits[37]; thus, more clinical trials are necessary for in-depth information on this topic, mainly in surgeries where much higher pain scores are expected.

Conclusions

The administration regimen of 16 mg of DXM + 1 g of Metamizole IV reduces immediate post-operative pain, up to the first 24 h, without increasing blood glucose levels of healthy patients undergoing ENT surgery.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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