Effectiveness of dexamethasone as an adjuvant in preemptive analgesia for postoperative pain in patients undergoing abdominal surgery

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Abstract

Objective: *To determine the effectiveness of adjuvant dexamethasone in preemptive analgesia for postoperative pain in patients undergoing abdominal surgery.* **Materials and methods:** *This was an experimental, comparative, prospective and longitudinal study. It included 92 patients scheduled for elective abdominal surgery, who participated with prior informed consent. They were divided in two groups of 46 patients. For statistical analysis of results, we used descriptive statistics and Chi square and Student t.* **Results:** *92 patients were evaluated with an average age of 47 years; 15% corresponded to ASA I, 56% ASA II, and 21% ASA III. With the visual analog scale (VAS), it was possible to observe that the mean difference between the groups was 0.91; both groups showed a minimum of zero and a maximum eight points. In comparison, we obtained $p < 0.05$ at the first hour, second hour, and at 24 hours of VAS assessment.* **Conclusion:** *Dexamethasone better controlled postsurgical pain and had adequate hemodynamic stability.*

KEY WORDS: *Dexamethasone. Postoperative pain. VAS.*

Introduction

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[1]. With this definition, the attention is directed to the nature of the pain suffered by a patient; pain is acknowledged as being more than a sensation subsequent to nociceptors physiological activation, and that includes emotional, cognitive and behavioral responses that are also influenced by psychological and social factors. Pain is always subjective and inalienable and, in consequence, assessing and treating it is our task[1,2].

Acute pain measurement, especially in the clinical setting, is carried out by means of a visual analog scale (VAS), which subjectively evaluates the intensity of perceived pain, both chronic and acute, allowing the patient to express the severity of his/her pain and enabling for a numeric value of it to be obtained: on a 0 to 9 scale the intensity of pain is indicated, with 0 being regarded as absence of pain and 9 as the worst possible pain[2].

The incidence of postoperative pain, regardless of the epidemiology in diverse populations, is generally regarded to be 100%, since there is no such thing as absolutely painless surgery. Postoperative pain is not a problem that should be taken lightly; its inadequate management can delay patient recovery, require hospital readmission or increase hospitalization time, in addition to causing an increase in health costs and reducing patient satisfaction. Postoperative pain adequate management increases patient quality of life[3].

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Postoperative pain is an acute pain with large repercussion, since it affects surgical patients, the family that suffers together with the patient, treating physicians, the rest of the health personnel that has to execute the indications for its treatment and the involved institutions. Postoperative pain relief constitutes a challenge for the professionals who comprise the surgical setting, and it was only until a few decades ago that passive attitudes were able to be dismissed to start addressing the problem at its entire magnitude[4].

The term "pain control" is applied to anesthesiology altogether, but at its current scope it refers to the management of pain beyond the operating room. The most effective approach to pain control must be multidisciplinary, where the patient is assessed by a physician who carries out an initial evaluation and formulates a treatment plan, and where services and resources of other specialists are usually available[4,5].

Pain is associated with autonomic, psychological and behavioral responses, elicited by noxious stimuli on the skin, somatic superficial, deep or visceral structures, or by muscular or visceral dysfunction. Adequate treatment of acute postoperative pain requires knowledge about its neurophysiology[2-4]. Pain is produced by hyperstimulation of the nociceptive pathways with great release of neuropeptides, neurotransmitters and prostaglandins, which are able to maintain peripheral and central nociceptors stimulation, as well as to create reflex muscular contractures, vicious circles and sympathetic vasomotor alterations. In addition, it conditions subsequent behaviors in case of a new intervention. Deficiency or absence of analgesia produces deleterious effects in the patient at the respiratory, cardiovascular and neuroendocrine systems. Surgical trauma and pain elicit an endocrine response that increases the secretion of cortisol, catecholamines and other stress hormones. Tachycardia, hypertension, decreased regional blood flow, immune response alterations, hyperglycemia, lipolysis and negative nitrogen balance are also produced[6]. All this plays an important role in postoperative period morbidity and mortality. By knowing the mechanisms by means of which pain is triggered, intervention plans can be created for its management by choosing the appropriate drugs[5,6].

As Wels mentions, given that postoperative pain has a multifactorial etiology, a multimodal treatment regimen makes sense[4-6]. Multimodal pain treatment is nothing but the combination of two or more drugs or analgesic methods intended to potentiate analgesia and reduce side effects. The analgesic ladder is the best demonstration of analgesics multimodal use, and it recommends progressive management of the different types with continuous pain assessment[4-6].

In 1988, Patrick Wall coined the term "pre-emptive preoperative analgesia". The word "preemptive", literally translated into Spanish means "preferential"; however, with this term, a movement to prevent acute and chronic postoperative pain was initiated[7]. The concept of preventive analgesia is used in anesthesiology and, more specifically, in the area of acute postoperative pain control by administering drugs before the nociceptive stimulus is produced[6,7]. It has evolved from pre-emptive analgesia, by changing the focus of attention from blocking the preoperative noxious stimulus, to a wider concept that involves blocking the noxious stimulus for the entire perioperative period[8]. A preventive analgesic effect is demonstrated when postoperative pain or analgesic consumption are reduced with regard to an intervention, if and when the effect is observed to exceed the drug's expected action time[6-8].

Katz[7] defines preventive analgesic effect as that which is demonstrated when 5.5 half lives of the analgesic are reduced. A preventive approach has the purpose to inhibit central sensitization, which results in postoperative pain lower intensity and lower analgesic requirement[7,8].

Several drugs are used for postoperative pain management: non-opiate analgesics such as non-steroid anti-inflammatory drugs (NSAID); opiate analgesics, which are associated with postoperative nausea and vomiting, sedation, itching and respiratory depression[6-8]; and diverse therapies, including cognitive-behavioral therapies and transcutaneous electrical nerve stimulation, which generally are used as adjuvants of pharmacological treatment to achieve a more comprehensive pain control. There is also the use of steroid therapy, the benefit of which has been demonstrated in numerous studies for pain and inflammation reduction in different surgical procedures, which range from third molar extraction to laparoscopic procedures[3-7]. They are known to reduce postoperative nausea and vomiting. They have been shown to elicit a high anti-inflammatory response by inhibiting the synthesis and release of pro-inflammatory and anti-inflammatory mediators. Corticosteroids possess the strongest anti-inflammatory properties of all steroids, as well as anti-hyperalgesic properties[8]. The representative of this group is hydrocortisone, which is the standard against which the pharmacological

properties of other synthetic steroids are compared, among which some have variations with regard to duration and strength[9]. In general, several routes of administration can be used. Those that are administered by the oral route are rapidly and almost entirely absorbed. The ester or water-soluble forms are administered by intravenous or intramuscular route in order for them to reach elevated systemic concentrations. The acetate forms are non-water soluble and can be exclusively administered by the intramuscular route. This route enables slow absorption, which prolongs their effect. They have a local inhibitory effect on signal transmission in nociceptive C-type fibers. They are associated with a reduction of analgesic drugs doses, which reduces the prevalence of their secondary effects[8,10,11].

Dexamethasone is a synthetic glucocorticoid with minimal mineralocorticoid activity. It is a potent anti-inflammatory, with 25-50-fold the activity of hydrocortisone and up to 16-fold higher than prednisolone[11]. It is commonly used in the perioperative period as prophylaxis for postoperative nausea and vomiting and reduction of airway and cerebral edema. It can be useful in the management of acute and chronic pain. Among its multiple actions, it reduces the release of bradykinin, tumor necrosis factor and interleukins 1, 2 and 6, as well as the production of prostaglandins. It also decreases impulse transmission in C-type fibers. Its half life is 3 hours, its action is more prolonged and has lower protein binding-affinity than other steroids. Its metabolism is hepatic, by glucuronidation, with inactive metabolites; 65% of the dose is excreted by the urinary route at 24 hours with less than 3% unaltered[11-13].

As an adjuvant, intravenously-administered dexamethasone has been shown to prolong regional anesthesia. When administered during general anesthesia, benefits have been shown in the reduction of postoperative pain if combined with NSAID, and with a decrease in opiate consumption[9-11]. It has been recommended as an adjuvant for cancer-origin pain therapy, particularly when there is presence of edema. Appropriate dose recommendations are variable in the literature on available studies, but single dose 4-8 mg or 0.05-0.5 mg per kg of weight doses have been shown to be effective to reduce postoperative pain and achieve lower opiate consumption[11-13].

Adverse effects associated with dexamethasone administration include perineal pain associated with the intravenous line, referred as a sensation of itching or even stabbing pain[11]. The incidence is unclear, but an occurrence range of 25-100%, higher risk in the female gender and an influence of drug administration rate is reported. The duration of this adverse effect ranges from 25 to 30 seconds[11-15]. There is good evidence in the literature about the beneficial effects of the use of dexamethasone as an antiemetic adjuvant in the perioperative period, particularly in combination with 5HT3 antagonists, in the management of acute pain and in the reduction of airway complications in patients with bronchial hyper-reactivity secondary to disease, smoking or airway manipulation; however, its effects in the perioperative period with regard to pain reduction are limited[11-18].

At the UMAE No. 25, in the surgery department, analgesic management is used in the preoperative and trans-operative periods. In the postoperative period, analgesia is administered at patient's request in the post-anesthetic recovery unit, under supervision of the specialist physician in charge of the area. There are no schematized protocols for the management of postoperative pain within the medical institution. Current incidence of postoperative pain remains elevated, at 35-45%.

It should be taken into account that postoperative pain intensity and duration in a patient are not accurately known. The incidence of postoperative pain, regardless of different populations' epidemiology, is generally 100%, since there is no such thing as an absolutely painless surgery. Its inadequate management delays the recovery period, produces an increase in health costs and reduces patient satisfaction.

Dexamethasone is administered for anti-inflammatory and antiemetic purposes, but not for its analgesia-related properties. It is necessary to have other type of drugs that can be implemented as adjuvants in preventive analgesia, in order to provide benefits in postoperative pain control and reduce analgesic requirements.

The purpose of this study was to determine dexamethasone efficacy as preventive analgesia for postoperative pain in patients intervened for abdominal surgery and to identify secondary effects occurring with the use of dexamethasone in patients intervened for abdominal surgery.

Material and Methods

This was an experimental, prospective, longitudinal clinical trial in adult patients programmed for elective abdominal surgery at the surgery area of the UMAE No. 25, in Monterrey, Nuevo León, Mexico.

Inclusion and exclusion criteria

- Age between 18 and 70 years.
- Either gender.
- Patients who accept the performance of the research.
- Patients with signed consent for the study.
- ASA I-II-II patients.
- Abdominal surgery.
- Electively programmed surgery.
- General balanced anesthesia.
- Patients belonging to the digestive surgery or onco-surgery departments.

Exclusion

- Patients with known allergic reaction to dexamethasone.
- Patients taking steroids prior to the surgical procedure.
- Patients with a potent opiate analgesic scheme prior to surgery.
- Patients with data consistent with serious metabolic or hemodynamic decontrol.

The sample size has a 95% confidence interval, heterogeneity of 50% and a margin of error of 5%, and a sample of 92 patients (46 per group) was therefore used.

The calculation was performed using the formula for finite populations:

$$N = z^2Npq / e^2(N - 1) + z^2pq$$

A simple random sampling was carried out, with patients participating in the clinical trial being consecutively distributed, one patient to each group (Y or Z) for the administration or not of adjuvant analgesia by randomly taking an envelope that was chosen by the physician anesthesiologist in charge to administer the analgesia at the operating room.

Collection sheets were used in the Excel program and grouped in central tendency and dispersion measures. The SPSSv20 program was used.

Results

Two groups of 46 patients each were analyzed; for this, the first one was administered 8 mg/2 ml of dexamethasone by the intravenous route, whereas the second group was administered only a placebo.

The study included 92 patients, among which median age was 47 years, with a recorded minimum of 22 years and a maximum of 70 years of age. With regard to patient gender, 50% were females and the other 50% were males (Table 1).

Based on the ASA classification, 16% were determined to correspond to ASA I, while 61% were identified in ASA II and, finally, 23% corresponded to ASA III (Table 1). Somatometric characteristics were also integrated to the statistical analysis, and weight in the dexamethasone group was observed to have a mean of 65 kg and mean height was 1.62 m. Mean weight of 69 kg and mean height of 1.67 m were observed in the placebo group.

On the other hand, heart rate distribution was assessed, with parameters being established by group: in the dexamethasone group, mean heart rate was observed to have a record of 69-71 beats per minute, with a minimum recorded of 54 and a maximum of 97, whereas in the placebo group, a mean of 70-74 beats per minute was observed, with a recorded minimum of 54 and a maximum of 97. When both groups were compared, the placebo group was determined to have had a wider distribution during the entire evaluation.

Assessment of the diastolic blood pressure determined a mean in the dexamethasone group of 70-73 mmHg, with a minimum of 57 and a maximum of 92; in the placebo group, a mean of 72-75 mmHg was identified, with a minimum of 58 and a maximum of 98. In the comparison between groups, the placebo group was observed to have a distribution with higher values for almost the entire evaluation, but at the end of the 2-hour period, the values were inverted and the dexamethasone group was observed to have slightly higher values.

In the dexamethasone group, systolic blood pressure had a mean of 119-121 mmHg, with a minimum of 80 and a maximum of 152. In the placebo group, a mean of 118-123 mmHg was recorded, with a minimum of 80 and a maximum of 150. In the comparative evaluation, a heterogeneous distribution is observed, with no predominance being established for neither group.

Mean oxygen saturation was estimated, and it was established to be 97% in the dexamethasone group, with a minimum of 94 and a maximum of 100; within the placebo group, the mean was established to be 97%, with a minimum of 94 and a maximum of 100. The comparative evaluation between groups established that the placebo group had higher oxygen saturation, but it should be noted that the difference was very small, barely 0.5.

The VAS integration determined a mean for pain in the dexamethasone group of 0-2, with a minimum

Table 1. Demographic, hemodynamic and pain assessment characteristics in 92 patients who were administered presurgical dexamethasone as adjuvant in postoperative analgesia

		Total (n = 92)	Dexamethasone (n = 46)	Placebo (n = 46)	p
Age (years)		47 ± 14	49 ± 15	45 ± 13	0.15
Gender					
Male		46 (50%)	20 (43%)	26 (57%)	0.29
Female		46 (50%)	26 (57%)	20 (43%)	0.29
Weight (kg)		67 ± 10	65 ± 9	69 ± 11	0.05
Height (cm)		165 ± 9	162 ± 8	167 ± 9	0.01
ASA	I	15 (16%)	7 (15%)	8 (17%)	0.22
	II	56 (61%)	25 (54%)	31 (67%)	0.21
	III	21 (23%)	14 (31%)	7 (16%)	0.18
SBP (mmHg)	PreSx	120 ± 12.04	122 ± 11.97	119 ± 12.12	0.17
	0 h	118 ± 13.96	119 ± 14.58	118 ± 13.35	0.91
	1 h	122 ± 13.67	122 ± 13.93	122 ± 13.42	0.86
	2 h	121 ± 13.83	120 ± 13.20	123 ± 14.47	0.69
	24 h	120 ± 10.93	120 ± 11.31	120 ± 10.55	0.96
	36 h	118 ± 11.17	119 ± 10.46	118 ± 11.89	0.52
DBP (mmHg)	PreSx	73 ± 8.73	72 ± 7.91	73 ± 9.56	0.59
	0 h	72 ± 8.99	70 ± 8.25	73 ± 9.74	0.11
	1 h	74 ± 8.30	73 ± 8.45	75 ± 8.16	0.30
	2 h	74 ± 9.19	72 ± 9.20	76 ± 9.18	0.04
	24 h	73 ± 8.62	73 ± 8.52	72 ± 8.73	0.71
	36 h	73 ± 8.34	73 ± 7.93	72 ± 8.75	0.73
Heart rate (bpm)	PreSx	70 ± 7.46	70±7.69	71 ± 7.23	0.70
	0 h	70 ± 7.17	69±7.34	70 ± 7.00	0.54
	1 h	72 ± 9.21	71 ± 9.97	74 ± 9.09	0.16
	2 h	72 ± 9.14	71 ± 9.33	73 ± 8.96	0.34
	24 h	71 ± 7.79	71 ± 8.13	71 ± 7.46	0.63
	36 h	70 ± 7.16	70 ± 7.31	71 ± 7.02	0.69
SpO_2 (%)	PreSx	97 ± 0.88	97 ± 0.84	97 ± 0.93	0.29
	0 h	97 ± 1.12	97 ± 1.19	97 ± 1.06	0.40
	1 h	98 ± 1.07	98 ± 1.12	98 ± 1.03	0.63
	2 h	98 ± 0.94	98 ± 0.96	98 ± 0.93	0.74
	24 h	98 ± 0.93	98 ± 0.95	98 ± 0.92	0.18
	36 h	98 ± 0.93	98 ± 0.92	98 ± 0.95	0.52
VAS (score)	PreSx	1 ± 1.47	1 ± 1.65	1 ± 1.18	0.02
	0 h	0 ± 0.84	0 ± 0.68	1 ± 0.97	0.46
	1 h	2 ± 2.50	1 ± 2.28	3 ± 2.65	0.08
	2 h	1 ± 2.08	0 ± 1.22	2 ± 2.51	0.01
	24 h	0 ± 0.84	0 ± 0.59	1 ± 0.99	0.01
	36 h	0 ± 0.23	0 ± 0.15	0 ± 0.02	0.65
Rescue dose		17 (26%)	7 (15%)	17 (37%)	0.25
Additional NSAID		11 (12%)	3 (7%)	8 (17%)	0.19
Nausea		7 (8%)	2 (4%)	5 (11%)	0.43

DBP: diastolic blood pressure; NSAID: non-steroid anti-inflammatory drugs; PreSx: presurgical; SBP: systolic blood pressure; SpO_2: oxygen saturation; VAS: visual analog scale.

recorded of 0 and a maximum of 8 points; the mean in the placebo group was recorded at 0-2.6, with a minimum of 0 and a maximum of 8 points.

In the dexamethasone group, ketorolac was administered only in three cases at 24 hours of the postoperative period, whereas in the placebo group it was administered more frequently, at 2 hours and subsequently at 24 hours, with a total of eight cases, thus demonstrating that the placebo group required administration of this drug in more occasions.

Administration of rescue doses in the dexamethasone group occurred at two different moments: at

hour 1 of the postoperative period, with five recorded cases and then at hour 2, with two recorded cases; in the placebo group, it had a distribution at hour 1 of the postoperative period, with 10 recorded cases, and 7 additional cases at hour 2 of the postoperative period. In the group comparison, it was evident that the placebo group had a larger distribution in rescue dose administration.

The distribution of postoperative symptoms demonstrated that there were no cases of vomiting recorded in both groups, while nausea occurred in two occasions in the dexamethasone group and in five in the placebo group.

The heart rate comparison by groups established that there were no statistically significant differences. The diastolic blood pressure assessment showed a very similar mean distribution in both groups, with a maximum difference of 3 mmHg; however, the only values that can be considered to be statistically significant are those recorded at hour 2 of the postoperative period, since a p-value of 0.04 was obtained. Systolic blood pressure had a slightly more homogeneous distribution, with the highest difference between groups being 1.5 at the end of assessment; however, none of the values obtained a statistically significant p-value.

Finally, the relationship between mean VAS scores was evaluated, and the largest difference between groups was determined to be 0.91 at 1 hour postoperatively; at the same time, VAS values at 1 hour, 2 hours and 24 hours were also identified to be statistically significant ($p < 0.05$).

Discussion

Pain is produced by hyper-stimulation of the nociceptive pathways with a great release of neuropeptides, neurotransmitters and prostaglandins, which are able to maintain peripheral and central nociceptors stimulation, as well as to create reflex muscular contractures, vicious circles and sympathetic vasomotor alterations. In addition, it conditions subsequent behaviors in case of new interventions[4,5]. Deficiency or absence of analgesia produces deleterious effects in the patient on the respiratory, cardiovascular and neuroendocrine systems. Surgical trauma and pain cause an endocrine response that increases the secretion of cortisol, catecholamines and other stress hormones. Tachycardia, hypertension, decreased regional blood flow, immune response alterations, hyperglycemia, lipolysis and negative nitrogen balance are also produced[6]. All this plays an important role in postoperative period morbidity and mortality. By knowing the mechanisms by means of which pain is triggered, intervention plans can be created for its management, with appropriate drugs being chosen[5,6]. Postoperative pain relief constitutes a challenge for the professionals who comprise the surgical setting, and it was only until a few decades ago that passive attitudes were able to be dismissed to start addressing the problem at its entire magnitude[4-6].

The literature claims that it is not possible for 100% absence of pain to exist, and clearly it is so, since although scores of 0 were found on several occasions within this investigation, mean VAS score was 0.04-2.19, which indicates that patients generally do experience at least minimum pain.

Dexamethasone administration could be considered to have interfered in the presence of pain, since the VAS tendency line was observed to have higher values in the control group in comparison with the dexamethasone group. Perhaps the difference between groups is not too large, but it was significant, which might generate a new line of investigation, focused especially on dexamethasone dosing, since the dose that was used this time was 8 mg, but if it was to be investigated in another occasion by creating two dexamethasone groups at different doses, higher certainty would be obtained on the efficacy of this drug.

Within the scientific literature, good results have been documented with regard to dexamethasone adjuvant effect. In a prospective, double blind trial, 106 women who underwent ambulatory gynecologic laparoscopy were randomized to receive saline or saline with dexamethasone at different doses (0.05 or 0.1 mg/kg) prior to general anesthesia induction[13]. The presence of postoperative pain, analgesic consumption, side effects and time to ambulatory department discharge were assessed[13]. It was concluded that dexamethasone offers dose-dependent effects with regard to postoperative recovery quality, and preoperative administration of 0.1 mg/kg of dexamethasone was shown to produce better recovery quality, with less postoperative pain and more promptness to return to usual activities, as well as an opiate-sparing effect[13].

Even when the reviewed articles have referred that adverse effects of dexamethasone administration are diverse, none of the mentioned adverse effects occurred in this study; furthermore, only a few patients experienced nausea, while in the rest, no other postoperative effect could be established.

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