

FENTANYL PRETREATMENT FOR ALLEVIATION OF PERINEAL SYMPTOMS FOLLOWING PREOPERATIVE ADMINISTRATION OF INTRAVENOUS DEXAMETHASONE SODIUM PHOSPHATE

A prospective, randomized, double blind, placebo controlled study

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Abstract

Background: Corticosteroids have anti-inflammatory, analgesic and antiemetic effects but causes severe perineal symptoms when given intravenously. Simultaneous administration of dexamethasone and fentanyl have been known to decrease the duration of perineal pain but its role in alleviating perineal pain has not been studied. Therefore, we hypothesized that fentanyl pretreatment could prevent the perineal symptoms associated with the dexamethasone.

Material and Methods: This prospective, randomized, double blind, placebo controlled study was done in 200 patients undergoing elective surgery requiring dexamethasone. The patients were randomized into two groups of 100 each. Group BD received 5 ml normal saline followed, 5 minutes later, by 8 mg dexamethasone bolus intravenously. Group FD received 1 µg/kg fentanyl diluted in saline to a volume of 5 ml followed by 8 mg dexamethasone bolus 5 minutes later. The time of onset, intensity, site, duration and nature of the pain after the drug administration were recorded.

Results: The demographic profile was comparable in the two groups. The incidence and severity of pain was more in females as compared to males (p value = 0). The pain was located especially in the perineal region and was expressed as itching (62%), burning (13%) or both (25%). The incidence of pain, its duration and severity were significantly reduced after pretreatment with fentanyl (p value = 0).

Discussion: Our study showed that the intravenous administration of dexamethasone sodium phosphate leads to significant perineal symptoms. These symptoms are alleviated by pretreatment with fentanyl (1 µg/kg) (incidence, severity and duration). The pharmacological mechanism explaining perineal pain with intravenous administration of dexamethasone remains poorly understood, but could be related to the phosphate ester.

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We conclude, that intravenous administration of dexamethasone sodium phosphate is associated with perineal pain and can be alleviated effectively by pretreatment with 1 µg/kg of fentanyl.

Key Words: Corticosteroids, Dexamethasone; Pain, Perineal; Fentanyl

Introduction

Corticosteroids play an important role in the perioperative period because of their diverse anti-inflammatory, analgesic and antiemetic effects¹⁻³.

Dexamethasone sodium phosphate is a water soluble inorganic ester of dexamethasone which is commonly used in the perioperative period because of its prolonged duration of action as well as lack of mineralocorticoid effect. In fact, it is now an established agent for the multimodal management of postoperative nausea and vomiting^{4,5}.

Timing of the treatment with dexamethasone is an integral part of the concept of preemptive analgesia and needs to be administered prior to anesthetic induction for its optimal effect⁶⁻⁹. This may be related to the presumed mechanism of action (on an intracellular receptor in the central nervous system), allowing sufficient time for dexamethasone to reach the effect site. Dexamethasone can be administered after induction of anesthesia, but this might limit the efficacy of dexamethasone to prevent postoperative nausea and vomiting as well as postoperative pain¹⁰.

However, one of the disadvantages of administering dexamethasone in the preinduction period is that it leads to severe perineal symptoms like pruritis, burning and pain following a bolus intravenous injection that could be very distressing for an awake patient.

Literature cites isolated case reports or case series related to perineal pain after intravenous administration of dexamethasone^{4,10-16}. Till to date there is no randomized controlled trial evaluating the perineal symptoms caused by the administration of intravenous dexamethasone. It has been reported that simultaneous administration of dexamethasone and fentanyl may reduce the duration of pain but its role in alleviating perineal pain has not been studied¹¹. Therefore, we hypothesize that the analgesic effect of

fentanyl, a potent opioid could prevent the perineal symptoms associated with the dexamethasone.

This study was planned to estimate the incidence of perineal symptoms (pruritis, burning, pain) after intravenous dexamethasone administered in the preoperative period and to evaluate the effect of fentanyl pretreatment for alleviation of these perineal symptoms.

Material and Methods

This prospective, double blind, placebo controlled, randomized study was done after obtaining the approval of the institutional ethics committee and a written informed consent from 200 ASA physical status I-III patients undergoing elective surgery at a tertiary care centre (All India Institute of Medical Sciences, New Delhi, India) requiring dexamethasone for multimodal management of postoperative nausea and vomiting (PONV) or postoperative analgesia.

A thorough preanesthetic work up of all patients with clinical evaluation and relevant laboratory investigations was carried out. Patients were eligible for participation, if they were more than 14 years of age and could cooperate and understand the Visual analogue score (VAS) scale. Only those patients, who were at increased risk for postoperative nausea and vomiting (laparoscopic procedures, gynaecologic procedures, middle ear surgery, and squint surgery) or in need for dexamethasone as multimodal analgesic requirement were included. Patients who were on regular medications with analgesic or analgesic use within 24 hours of anesthesia, drug or alcohol abuse, contraindications to steroid use [diabetes mellitus / impaired glucose tolerance, peptic ulcer disease, endocrine disorder, morbid obesity (BMI >30)] were excluded from the study.

Patients were explained about the use of VAS for grading the severity of pain on a scale of 0 to 10.

In the operating room, after attaching routine monitors (ECG, non invasive blood pressure, pulse oximeter), an 18 G intravenous cannula was secured on the dorsum of the left hand.

The patients were randomized into two groups of 100 each based on computer generated random number list.

(I) Group BD: Intravenous administration of 5 ml normal saline followed by 8 mg dexamethasone bolus 5 minutes later.

(II) Group FD: Intravenous administration of 1 µg/kg fentanyl diluted in saline to a volume of 5 ml followed by 8 mg dexamethasone bolus 5 minutes later.

The randomization was not disclosed to any of the personnel (those administering drugs, those observing study parameters, data analysts) or the patient throughout the study. An independent investigator not involved in the observation prepared the study drug. The effects of the drugs were observed by an investigator who was unaware of the drugs administered. The patient was observed for the next ten minutes and the rest of the anesthetic procedure was allowed to proceed.

The following parameters were recorded continuously following the drug administration:

- The time of onset and intensity (VAS) of the perineal symptoms after the end of the drug administration.

- The site of pain or other symptoms.
- The duration of the symptoms.
- The nature of the symptoms (pruritis, burning, pain).

In the absence of any previous study, the sample size was calculated based on the case series by Perron et al⁴ with perineal symptoms as primary outcome and with an aim of 50% decrease in the symptoms with pretreatment with fentanyl, with a power of 90% and α -0.05.

The comparison of sex and occurrence of pain was carried out using chi square test. The age, weight, onset and duration of pain and VAS was compared using independent t test. The p value <0.05 was taken as significant.

Results

A total of 227 patients were assessed for eligibility and 200 patients were enrolled in the study (Fig. 1).

The demographic profile was comparable in the two groups (Table 1).

Fig. 1
Flow chart showing patient enrollment for the study

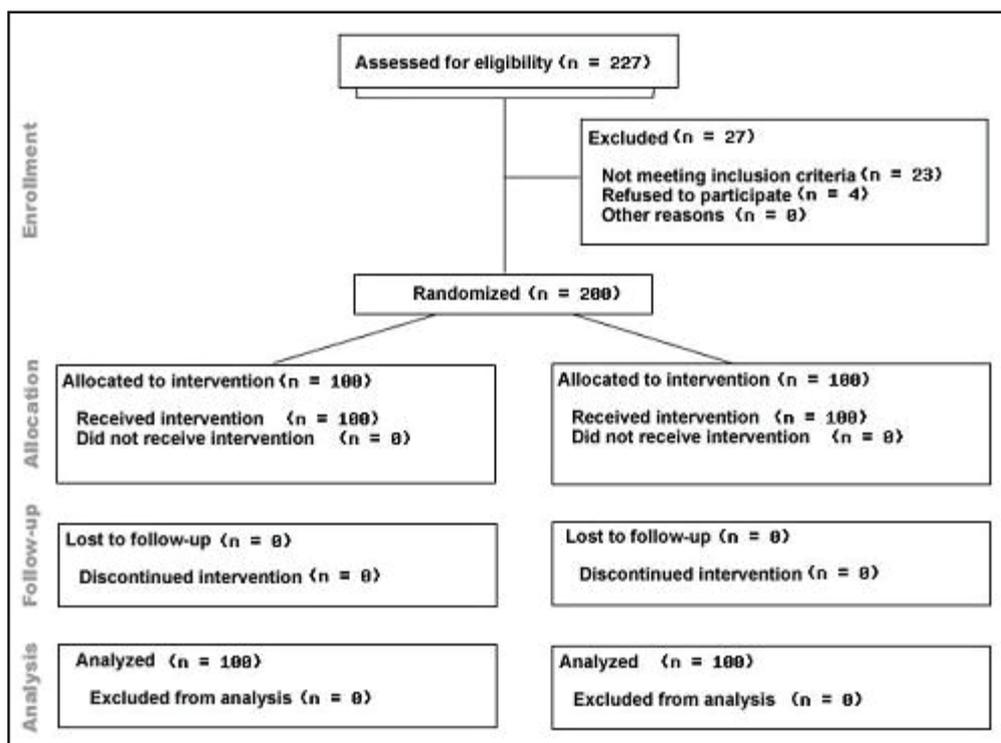


Table 1
Demographic Profile

	Group BD (n=100)	Group FD (n=100)	P value
Age (years)	35.6 ± 12.9 (14-75)	35.8 ± 11.4 (14-65)	0.906
Sex (M:F) (%)	40:60 (40:60)	38:62 (38:62)	0.085
Weight (kg)	58.3 ± 10.5 (37-93)	59.3 ± 9 (38-80)	0.487

Values as mean ± SD (Range)

The incidence and severity of pain was more in females as compared to males (p value 0.001) (Table 2).

The pain was located especially in the perineal region and was expressed as itching (62%), burning (13%) or both (25%). One patient mentioned generalized tingling sensation all over the body and another patient reported dizziness. The incidence, duration and severity of the perineal symptoms were significantly reduced following pretreatment with fentanyl (p value 0.001) (Table 3).

Discussion

Our study showed that the intravenous administration of dexamethasone sodium phosphate causes pain and itching in the perineal region. These symptoms were observed to be more severe and of a longer duration in females as compared to males. The pretreatment with fentanyl in a dose of 1 µg/kg reduced the pain and itching (incidence, severity and duration) caused by intravenous administration of dexamethasone.

Table 2
Incidence of dexamethasone induced pain among males and females

	Male (n = 40)	Female (n = 60)	P value
Pain (n) (%)	15/40 (37.5%)	56/60 (93.3%)	0.001
Pain Onset (sec)	25.7 ± 7.3 (20-40)	24.3 ± 7 (10-45)	0.505
Pain Duration (sec)	28.7 ± 19.2 (10-80)	77.8 ± 31 (21-120)	0.001
Pain VAS (median)	4 (3-6)	7 (4-9)	0.001

Values as mean ± SD (Range) or as otherwise stated

Table 3
Effect of Fentanyl pretreatment on pain with intravenous dexamethasone

		n	Group BD	n	Group FD	P value
P a i n p e r c e i v e d (n) (%)	Total	100	71/100 (71%)	100	25/100 (25%)	0.001
	Male	40	15/40 (37.5%)	38	0/38 (0%)	0.001
	Female	60	56/60 (93.3%)	62	25/62 (40.3%)	0.001
P a i n O n s e t (sec)	Total	100	24.6 ± 7 (10-45)	100	17.6 ± 6 (10-35)	0.001
	Male	40	25.7 ± 7.3 (20-40)	38	-	-
	Female	60	24.3 ± 7 (10-45)	62	17.6 ± 6 (10-35)	0.001
P a i n D u r a t i o n (sec)	Total	100	67.4 ± 35.2 (10-120)	100	11.6 ± 4 (5-20)	0.001
	Male	40	28.7 ± 19.2 (10-80)	38	-	-
	Female	60	77.8 ± 31 (20-120)	62	11.6 ± 4 (5-20)	0.001
P a i n V A S (median)	Total	100	7 (3-9)	100	2 (1-3)	0.001
	Male	40	4 (3-6)	38	0	0.001
	Female	60	7 (4-9)	62	2 (1-3)	0.001

Values as mean ± SD or otherwise as stated

The pharmacological mechanism explaining perineal pain with intravenous administration of dexamethasone remains poorly understood, but could be related to the phosphate ester of the corticosteroid (dexamethasone sodium phosphate) since perineal irritation has been described with hydrocortisone-21-phosphate sodium and prednisolone phosphate as well^{4,11,12,15}. The symptoms lasted only for a short period till the drug was hydrolysed into phosphate ions and dexamethasone.

Opioids (fentanyl, remifentanyl, alfentanil, tramadol) have been used to alleviate the pain of propofol intravenous administration^{17,21}.

Opioid receptors are found in the dorsal root ganglia, the central terminals of primary afferent nerves and peripheral sensory nerve fibres and their terminals. Opioids show their effects either centrally or peripherally. The reduction in pain due to propofol injection has been attributed to the interaction with peripheral m-opioid receptors^{17,22}. It has also been suggested that prevention of propofol injection pain by opioids may be mediated via central opioid receptors²¹.

In view of propofol pain being decreased by pretreatment with opioids, we thought of using it for alleviating pain with dexamethasone administration.

Of interest in the perioperative setting is the decreased release of bradykinin, tumour necrosis factor, interleukin-1, interleukin-2 and interleukin-6 and decreased production of prostaglandins after administration of steroids. There is decreased transmission of impulses in C fibres²³. So, we think that fentanyl probably acts via central action for alleviating dexamethasone pain.

Adverse effects reported in association with dexamethasone include perineal pain associated with intravenous injection. The incidence of this complication is unclear, with females at increased risk compared to men. The speed of injection and the dose may also influence the severity.

Epidural administration of dexamethasone has not been associated with perineal pain²⁴.

Each milliliter of dexamethasone sodium phosphate injection, 4 mg/mL, contains dexamethasone

sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. The pH of both concentrations is 7.0-8.5. Other ingredients include methylparaben and propylparaben added as preservatives. The implication of methylparaben, propylparaben for causing perineal pain has not been reported^{25,26}.

The type of pain mentioned includes itching, burning and squeezing¹¹. Perron reported perineal burning, itching and tingling after intravenous dexamethasone⁴. In our study, we observed the symptoms as burning and itching mainly and one patient complained of tingling and dizziness.

Various measures to prevent perineal discomfort include administration of dexamethasone after induction of anesthesia, dilution of dexamethasone and giving it as a slow bolus^{11,12,14,27}. Most of the effects of glucocorticoids are mediated through an altered protein synthesis³. So, onset of biological action is generally one to two hours. Wang et al designed a study to test the hypothesis that dexamethasone was more effective in preventing PONV when administered before the induction of anesthesia than at the end of anesthesia⁷. They observed that the administration of dexamethasone at the end of anesthesia did not provide an effective antiemetic effect during the immediate postoperative period of 0-2 hours. Based on this finding, they suggested that the onset time of dexamethasone antiemetic effect may be approximately two hours⁶.

Though dexamethasone can cause side effects such as increased incidence and severity of infection, adrenal suppression and delayed healing in surgical patients, a single dose has not been reported to cause any such adverse effects^{3,29-31}.

Our study is limited by the fact that the use of fentanyl as pretreatment for alleviating dexamethasone pain can be used in the perioperative settings where fentanyl is a part of anesthetic management. Its use cannot be justified in other settings where dexamethasone is being used such as chemotherapy.

We conclude, intravenous administration of dexamethasone sodium phosphate is associated with perineal pain which can be alleviated effectively by pretreatment with 1 µg/kg of fentanyl.

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