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Low Dose Dexamethasone Reduces Spinal Buprenorphine Associated Nausea and Vomiting

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Abstract

Background: Intrathecal Buprenorphine is an adjuvant to spinal anaesthesia offers the advantage of providing good analgesia, but is associated postoperative nausea and vomiting. Dexamethasone is a potent steroid and has good antiemetic effect. The aim of this randomized controlled trial was to compare the antiemetic efficacy of dexamethasone 4 and 8mg. *Methods:* 180 patients of either sex undergoing elective lower extremities and infra umbilical surgeries were included in the study. The patients in group D0, D4 and D8 received 5ml normal saline, 4 mg and 8mg dexamethasone respectively before spinal anaesthesia. Spinal anaesthesia was established with a single bolus of 0.5% hyperbaric bupivacaine 15 mg and buprenorphine 60mcg. The primary end point of this study was the total nausea and vomiting rate for 8 hours post spinal anaesthesia. The secondary end points were the incidence of nausea, vomiting and the occurrence of adverse events like pruritis. *Statistical Analysis:* The incidence of nausea, vomiting and pruritus was analyzed using a series of 3×2 $\chi 2$ tests. *Results:* Demographic profile was similar between the groups. The incidence of nausea was 16% in group D0 and was 5% in the groupD4 and D8. The incidence of vomiting was 5%, 3.3%and 1.7% in the D0, D4 and D8 groups respectively. The incidence of nausea and vomiting was not very different in the D4 and D8 groups. *Conclusions:* Both doses of prophylactic dexamethasone 4/8 mg significantly reduces the nausea and vomiting associated with intrathecal Buprenorphine. A dose of 4mg of dexamethasone is as efficacious as 8mg.

Keywords: Buprenorphine; Dexamethasone; Intrathecal Opiates; Nausea and Vomiting.

Introduction

Opioids are potent centrally acting analgesic drugs for the treatment of pain. The discovery of spinal opioid receptors has led to the use of spinal opioids to produce dense segmental analgesia that is devoid of the dose-limiting side effects associated with systemic opioid administration [1]. Buprenorphine is a long acting, highly lipophilic opioid, which has proved to be an excellent analgesic adjuvant for neuraxial blocks. Intrathecal Buprenorphine as an adjuvant to spinal anaesthesia offers the advantage of providing good analgesia whilst allowing early ambulation of the patient by sparing sympathetic and motor nerves [2-7]. The use of Buprenorphine has been associated postoperative nausea and vomiting the incidence of which has been found to be as high as 34% [2,4].

Dexamethasone is a potent steroid and has good antiemetic effect [8]. The combination of low cost and apparent safety makes dexamethasone a first-line agent for prophylaxis against postoperative nausea and vomiting (PONV) [9]. The Society for Ambulatory Anaesthesia (SAMBA) guidelines for the management of PONV recommends a prophylactic dose of 4 mg to 5 mg for patients at high risk of PONV regardless of the surgical procedure [10]. There are some studies that have used 8mg of dexamethasone for PONV prophylaxis and treatment, it has been found to have additional

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benefits like it improved post discharge quality of recovery in addition to reducing nausea, pain, and fatigue [11-13]. There are no studies on the use of dexamethasone for prevention of PONV associated with intrathecal buprenorphine. The aim of this randomized controlled trial was to compare the antiemetic efficacy of dexamethasone 4 and 8mg, when compared with placebo in the prevention of nausea and vomiting associated with intrathecal buprenorphine.

Material and Methods

A prospective placebo controlled study was conducted in 180 patients of either sex undergoing elective lower extremities and infra umbilical surgeries. The patients of American Society of Anaesthesiologists(ASA) Grade 1-3 aged between 18-70 years were included in the study. Patients who had steroid use within last 48 hours, allergy to dexamethasone and intraopertative conversion to general anaesthesia were excluded from the study. The patients satisfying the inclusion criteria was selected by random number table during the study period from the operation theatre register on a daily basis. Institutional ethical clearance was obtained and after obtaining a written informed consent the patients were allotted into three groups of 60 each. The patients in group D0 received 5ml normal saline, the patients in groups D4 received 4 mg dexamethasone and patients in groups D8 received 8mg dexamethasone.

All the patients received oral pantoprazole 40mg as premedication. Perioperative monitoring included electrocardiogram, non-invasive blood-pressure monitor and pulseoximetry. An 18-gauge IV cannula was inserted, and normal saline infusion was instituted. Midazolam 1 mg was administered following placement of intravenous line. The study drugs were prepared, diluted to 5 ml with normal saline and was administered by slow (over 30 seconds) intravenously immediately before performing spinal anaesthesia by an independent investigator not involved in the further management of patient. Patients, anaesthesiologists involved in intraoperative care, and investigators who will collect postoperative data were blinded to patient group allocation.

A standardized anaesthetic technique was followed. Anaesthesia was instituted in the sitting position using an aseptic technique, a 25-gauge Quinke needle was inserted via a midline approach into the L2-3 or L3-4 interspace. Anaesthesia was established with a single bolus of 0.5% hyperbaric bupivacaine 15 mg and buprenorphine 60mcg. The level of sensory blockade was assessed regularly by the level of touch sensation before surgical incision (T6-8 was considered adequate). Additional midazolam 1–2 mg iv was administered for intraoperative sedation on attending anaesthesiologist's discretion.

Supplemental oxygen 5 L/min via a facemask was administered during the surgery. Estimated fluid requirement and maintenance fluid were replaced with ringer latacte or 0.9% normal saline. A standard postoperative analgesic regimen of Paracetamol 1 gram iv infusion 6th hourly and tramadol 50 mg intramuscularly as required was prescribed for postoperative pain relief.

The primary end point of this study was the total nausea and vomiting rate for 8 hours post spinal anaesthesia. The secondary end points were the incidence of nausea, incidence of vomiting and the occurrence of adverse events like pruritis or any other adverse events in 8 hours following spinal anaesthesia. All episodes of nausea or vomiting were recorded during the first 8 hours after anesthesia. An investigator, who was blinded to the study group allocation asked patients if vomiting had occurred and if they felt nauseated. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. Ondansetron 4mg was administered intravenously as a rescue antiemetic drug when patients had a nausea or when they experienced vomiting, or at the patient's request.

Statistical Methods

Sample size calculation: Sample size calculation was performed before starting the trial by using a statistical power analysis. The incidence of PONV following intrathecal buprenorphine was found to be 25% in a study by Khan et al, expecting a 75% reduction in the PONV in the dexamethasone group, based on an α error of 0.05 and power of the study to be 80%, the sample size was estimated to be 57 in each group [11]. To compensate for patients not completing the study or loss of data, we randomized 60 patients to each group. The Parametric data were analyzed by using analysis of variance. The incidence of nausea, vomiting and pruritus was analyzed using a series of 3×2 $\chi 2$ tests to determine differences among the three groups, followed by 2×2 $\chi 2$ tests for intergroup differences. A p value < 0.05 was considered statistically significant.

Results

A total of 180 patients were enrolled in the study, the patient characteristics, ASA physical status grade and surgical duration was similar between the three groups (Table 1). The incidence of nausea was 16% in the saline group (D0) and was only 5% in the groups that received dexamethasone (D4 & D8). The incidence of vomiting was 5%, 3.3% and 1.7% in the D0, D4 and D8 groups respectively. As the numbers were very small for comparison between the groups, the total incidence of nausea and vomiting were compared between the groups and was found to be significant (p=0.0228). Intergroup comparison was then done, the group D0 had a 21.7% incidence of nausea and vomiting. The groups that received dexamethasone D4 and D8 had a significantly reduced incidence of nausea and vomiting at 8.3% and 6.7% respectively (Figure 1). The groups D4 and D8 had a 61.5% and 69.23% reduced incidence of nausea and vomiting compared to the placebo group. The incidence of nausea and vomiting was not very different in the D4 and D8 groups(p=0.7289). The incidence of pruritis was not very different between the groups (Table 2). One patient in the D8 group had severe vomiting that only subsided with ondansetron 8 mg and metaclopramide 10 mg.

Table 1: Demographic data

	D0	D4	D8	P value
Age in years	52.60 ± 14.35	53.72 ± 12.05	54.15 ± 13.66	.808
Sex	Male 75% female 25%	Male 63.3% female 36.7%	Male 68.3% female 31.7%	.383
Weight in kg	65.81±8.20	67.06±9.15	63.38±9.02	0.066
Duration of surgery(minutes)	70.83 ±31.32	71.75 ± 29.10	66.32±28.56	.563
ASA grade I	60 %	60%	59.4%	.977
II	40%	40%	40.6%	

Data are presented in Mean ± standard devaition

Table 2: Incidence of Nausea, vomiting and pruritis

	D0	D4	D8
Nausea	10(16.7%)	3(5%)	3(5%)
Vomiting	3(5%)	2(3.3%)	1(1.7%)
Total	13(21.7%)	5(8.3%)*	4(6.7%) †
Pruritis	6(10%)	5(8.3%)	6(10%)

*P value = 0.0408 significant between D0 and D4 † P value =0.0184 significant between D0 and D8

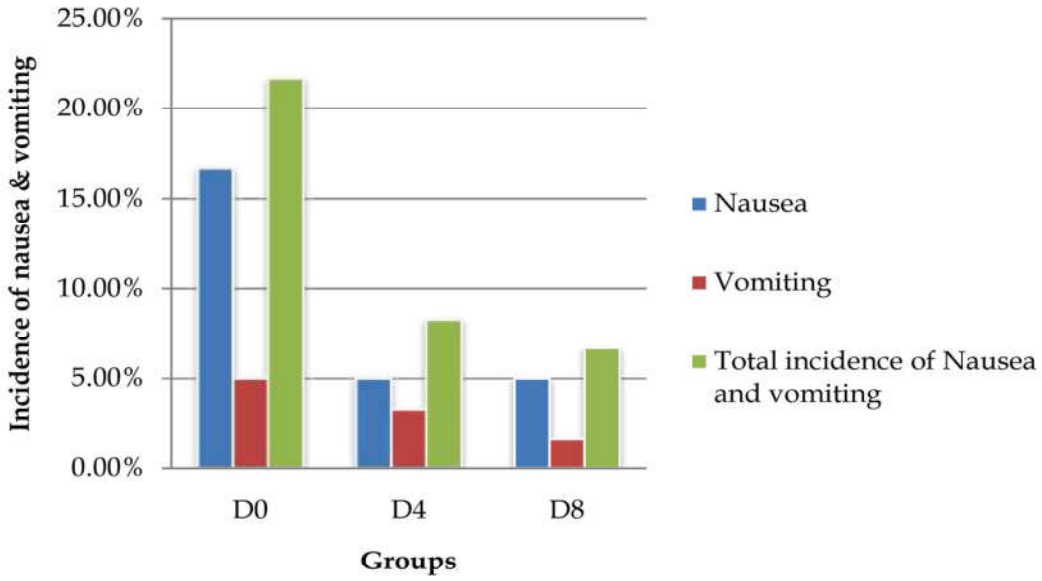

Fig. 1: Incidence of Nausea, vomiting and pruritis

Discussion

Neuraxial opioids are commonly used for providing postoperative analgesia and have many advantages over parentral narcotics. Although intrathecal opiates are an excellent means of providing post operative analgesia, but have troublesome side effects like nausea, vomiting and pruritis [1].

In the present study we found the incidence of nausea and vomiting following intrathecal buprenorphine to be 21.7% when no prophylactic dexamethasone was administered. Both doses of prophylactic dexamethasone 4/8 mg were effective in reducing the intrathecal bupernorphine associated nausea and vomiting, but had no effect on the incidence of pruritis.

Dexamethasone is used as an antiemetic in patients receiving highly emetogenic chemotherapy [14]. It has been found to significantly reduce the incidence of PONV. A prophylactic dose of 4 to 5 mg IV for patients at increased risk for PONV is recommended by SAMBA.[15] The efficacy of dexamethasone 4 mg IV for PONV prophylaxis has been found similar to ondansetron 4 mg IV and droperidol 1.25 mg IV [10].

Dexamethasone has been used for PONV prophylaxis following spinal anaesthesia. Khatiwada N et al. in a study involving patients undergoing total abdominal hysterectomy under subarachnoid block found that dexamethasone 4 mg group had a 40% incidence of nausea and vomiting, whereas the placebo group had an incidence of 67.5%.[16].

On review of literature on the use of dexamethasone to prevent intrathecal opiate induced nausea and vomiting, we found conflicting results. Wu et al. reported that dexamethasone alone was not an effective antiemetic but a combination of dexamethasone 4 mg and droperidol 6.25 mg reduced the incidence of PONV after spinal morphine 0.2 mg for cesarean section compared with placebo [17].

Szarvas et al. found that dexamethasone 8 mg IV plus ondansetron 8 mg was as effective as ondansetron 8 mg. The administration of dexamethasone alone was associated with a frequent incidence of PONV, demonstrating a lack of efficacy when used alone in the prophylaxis of PONV in patients undergoing major orthopedic operation with spinal morphine [18]. The incidence of PONV associated with intrathecal morphine has been found to be as high as 73% [19]. This high incidence of PONV is probably associated with failure of dexamethasone in preventing nausea and vomiting episodes. Whereas incidence of nausea and vomiting following intrathecal buprenorphine has been considerably less at around 20-34% which is similar our findings where the incidence was 21.7% [4,5].

When given as a single drug or when used in combination therapy, 4 mg to 5 mg of dexamethasone has been found to have comparable clinical effects on the prevention of PONV as the 8-mg to 10-mg dose [20].

Allen TK et al. in a systematic review found relatively strong evidence that a single IV dose of dexamethasone 5 to 10 mg was an effective antiemetic for women receiving neuraxial morphine for cesarean delivery or abdominal hysterectomy [21]. Wang et al suggested that dexamethasone, 5 mg iv is the minimum effective dose in preventing nausea and vomiting associated with epidural morphine for post-Cesarean analgesia [22]. The exact mechanism by which dexamethasone exerts an antiemetic action is not fully understood. But its antiemetic action may be via the blockage of the receptors in the nucleus tractus solitarius of the central nervous system. Dexamethasone may also exert its antiemetic action through some peripheral mechanism [23].

The possible mechanisms for antiemetic effect of corticosteroids are it may affect 5-hydroxytryptamine (5HT) turnover in the in neural tissue by shunting the metabolism of tryptophan away from 5-HT pathways and it may prevent the release of 5-HT in the gut or prevent activation of 5-HT receptors in the gastrointestinal system [24].

Dexamethasone had no effect on the incidence of pruritis, the incidence of which in our study was similar to the findings of other studies [18,21,25]. Our study has a few limitations, firstly we have only studied the incidence of PONV in the first eight hours, although few studies have found dexamethasone to have a delayed antiemetic as effect we found protocol violations were common in our pilot study postoperatively after eight hours. Secondly we have not studied the patient satisfaction or potentiation of analgesic effects. Lastly, we have compared two doses of dexamethasone and comparison with another class of antiemetic would have improved the study.

We conclude that dexamethasone significantly reduces the nausea and vomiting associated with intrathecal buprenorphine. A dose of 4mg of dexamethasone is as efficacious as 8mg and is a low cost alternative to other antiemetic drugs.

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