IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 9 Ver. X (September. 2017), PP 72-76
www.iosrjournals.org

Comparison of Ondansetron with combination of ondansetron and dexamethasone for prevention of nausea and vomiting after Carboprost in LSCS patients under spinal anesthesia

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Abstract
Introduction : *Carboprost is used to prevent and treat postpartum hemorrhage in pregnant patients, however it is associated with severe nausea and vomiting .This is quite discomforting for the patient and the treating obstetrician. This study was designed to compare ondansetron only and ondansetron along with dexamethasone for the prevention of Carboprost induced nausea and vomiting*
Materials and Methods*: This double blinded study Was done at a peripheral hospital from July 2016 to July 2017.200 ASA Class I and II full-term pregnant patients scheduled for elective LSCS were randomly allocated into two groups namely group O and group OD Inj.carboprost 250 mcg was given intramuscularly after the delivery of anterior shoulder in both groups.Inj ondansetron 4 mg and Inj dexamethasone 4mgsIV with ondansetron4mgs was given respectively to both groups. Patients were observed intraoperatively and in the recovery room and ward for any episodes of nausea and vomiting. Rescue antiemetic was given if the patient had PONV score of 2 and was also recorded.*
Results: *The severity of nausea in immediate postoperative period was significantly less in theOD group compared to O group (p value0.0010)The incidence of post op nausea and vomiting is significantly lower in the OD group than in O group 43 (43%) Vs 55 (59%) p value of 0.036 in 0-6 hrs. and also overall in 0-24 hours 59(63%) Vs 45(45%) p value of 0.016. The incidence of rescue antiemetic used was significantly lower in the OD group than in the D group during the 0-6 hours after the operation (13 vs. 24%) (P = 0.043). Incidence of side effects (headache, constipation and dizziness) was comparable in both the groups.*
Conclusion: *We conclude that Combination of Dexamethasone and ondansetron in comparison to ondansetron alone, decreases the overall incidence of carboprost induced nausea and vomiting in the immediate postoperative period*
Keywords: *Carboprost, Cesarean section, , Dexamethasone, Ondansetron.,PONV(Post OP Nausea Vomiting)*

Date of Submission: 15 -09-2017 Date of acceptance: 30-09-2017

I. Introduction

Nausea and Vomiting is a frequent adverse effect seen with administration of carboprost tromethamine[1] – a medication used to prevent/control postpartum hemorrhage. In spite of administration of potent antiemetic this side effect is difficult to control. Incidence of nausea is about 1/3 patient while vomiting is about 2/3 patients in LSCS patients in which carboprost was given IM (intramuscular).Many drugs are used for management of PONV but few of them have side effects like sedation, dysphoria, extrapyramidal symptoms, and dryness of mouth, restlessness and tachycardia. 5HT3 receptors antagonists are devoid of such side effects. Ondansetron, granisetron and newer drug such as ramosetron and palonosetron are commonly used drugs to prevent PONV[2.] Dexamethasone is a corticosteroid with antiemetic and high anti-inflammatory effects. Use of dexamethasone in combination with the other drugs has been reported to increase the antiemetic or analgesic efficacy, and minimal side effects have been reported when it is used as a single agent. The mechanism for the antiemetic effect of dexamethasone has been incompletely understood but it is thought to be caused by the inhibition of prostaglandin synthesis, by showing anti-inflammatory efficacy and by causing a decrease in the release of endogenous opiates. Since nausea and vomiting can occur by a variety of different mechanisms, combinations of different antiemetic are used to prevent or treat these symptoms.

Effect of addition of dexamethasone to ondansetron in the control of postoperative nausea and vomiting (PONV) has been studied before[3], but we could not find any study in the literature that investigated the efficacy of this after carboprost administration for the control of post-delivery PONV. This study was aimed to

compare the antiemetic efficacy of ondansetron and dexamethasone combination with that of the single use of ondansetron to decrease the incidence of PONV during CS under spinal anesthesia.

II. Materials And Methods

This prospective, randomized, double blind study was carried out after approval from institutional ethics committee in 200 patients of age group 20-35 years and ASA physical status of grade I and II scheduled for LSCS with use of carboprost IM under spinal anesthesia in aperipheral hospital. Exclusion criteria were emergency cesarean section, known allergy to any of the medications, abnormal liver and renal function tests, history of motion sickness or migraine, severe cardiac disease,GDM, history of maternal smoking and known asthma or epilepsy. Informed written consent was obtained. They were pre-medicated with inj. ranitidine 50mgs IV half an hour before surgery and randomly allocated into two groups.Group O and group OD inj. ondansetron 4 mg and inj. Dexamethasone 4 mg IV with ondansetron was given respectively at time of induction of anesthesia. All the patients were pre-loaded with inj. RL 10 ml/kg to prevent intraoperative hypotension followed by nausea and vomiting. Spinal anesthesia was instituted with 2.2 ml of 0.5% Bupivacaine with 25 gauge spinal needle.

Standard American Society of Anesthesiology monitoring was done. In both the groups carboprost 250 µg was administered intramuscularly after the delivery of anterior shoulder of baby along with oxytocin 10 units in infusion. Patients were observed intraoperatively and in the recovery room and ward for any episode of nausea and vomiting. Rescue antiemetic inj. metoclopramide 10 mg IV was given if the patient had more than 2 episodes of vomiting and was also recorded. The primary outcome was taken as PONV during first 0-6 hrs, the secondary outcome incidence of PONV 6-24 hours and 0-24 hr. in combination was taken. The severity of nausea, use of rescue antiemetic and patient satisfaction were also studied as secondary outcomes. The sample size was calculated according to the incidence of PONV which was high as 80% with use of carboprost .Statistical analysis was performed using SPSS for windows. The students t-test was used to compare variable between groups Categorical variables were analyzed using the $\chi 2$ test or Fisher's exact test, as appropriate. A P value of < 0.05 was considered statistically significant. Data are presented as means ± standard deviation (SD), numbers, or percentage.

III. Results

All total 200 patients initially selected in the study. However 7 patients were excluded from the study as they developed vomiting before administration of the drug. Data obtained from the remaining 193 patients were analyzed, with 94 patients in the O group and 99 patients in the OD group. The demographic data with respect to age, sex, height and weight were comparable in both the groups (Table 1) The severity of nausea during the 2-6 hrs post operatively was significantly less in the OD group p=0.010(table 2).The incidence of post op nausea and vomiting is significantly lower in the OD group than in O group 43(43%) Vs 55(59%) p value of 0.036 in 0-6 hrs and also overall in 0-24 hours 59(63%) Vs 45(45%) p value of 0.016. The incidence of rescue antiemetic used was significantly lower in the OD group than in the D group during the 0-6 hours after the operation (13 vs. 24%) (P = 0.043) Headache occurred more frequently in the OD group than group O, but it is not statistically significant (p=0.067) (Table 2).

Demographic profile (Table 1)

	Group O(n=94)	**Group OD(n=99)**	**P**
Age(years)	24.69 ± 2.72	24.33 ± 2.58	P >0.05, NS
Height(cm)	157.45 ± 9.63	154.38 ± 8.96	P >0.05, NS
Weight(kgs)	64.3 ± 4.7	65.1 ± 4.9	P >0.05, NS
Duration Of Surgery(mins)	83.19 ± 8.76	85.34 ± 9.12	P >0.05, NS
Asa status(1,2)	76,18	84,15	P >0.05, NS

Severity of Nausea 0-24 hrs (Table 2)

	O group (n = 94)	**D group (n = 99)**	**P values**
0-2 h			
None	51 (54%)	61(62%)	0.125
Mild	10 (11%)	12 (12%)	
Moderate	6 (6%)	9 (9%)	
Severe	27 (29%)	17 (17%)	
2-6 h			
None	63(67%)	79 (80%)	0.010
Mild	9 (10%)	10 (10%)	
Moderate	5 (5%)	4 (4%))	
Severe	17 (18%)	6 (6%)	

6-24 h			
None	72 (77%)	83 (84%)	0.606
Mild	13 (14%)	5 (5%)	
Moderate	4 (4%)	6 (6%)	
Severe	5 (5%)	5 (5%)	

Incidence Of PONV And Use Of Rescue Anti Emetics During First 24 Hours(Table 3)

	O group (n = 94)	**OD group (n = 99)**	**P values**
0-2 h			
Nausea	43 (46%)	38 (38%)	0.300
Vomiting	14 (15%)	10 (10%)	0.313
PONV	43 (46%)	38 (38%)	0.300
Rescue antiemetic	23 (24%)	13 (13%)*	0.043
0-6 h			
Nausea	55 (59%)	42 (42%)*	0.025
Vomiting	20 (21%)	16 (16%)	0.362
PONV	55 (59%)	43 (43%)*	0.036
Rescue antiemetic	29 (31%)	21 (21%)	0.127
0-24 h			
Nausea	59 (63%)	44 (44%)*	0.011
Vomiting	23 (24%)	18 (18%)	0.286
PONV	59 (63%)	45 (45%)*	0.016
Rescue antiemetic	31 (33%)	21 (21%)	0.066

Incidence of Adverse effect (0-24Hrs) Table 4

Adverse effects	**O group (n = 94)**	**OD group (n = 99)**	**P values**
Dizziness	17 (18%)	19 (19%)	0.844
Headache	10 (11%)	20 (20%)	0.067

IV. Discussion

There was no definite study performed regarding comparison of ondansetron and dexamethasone after use of carboprost in LSCS. In our setup, we have observed number of patients who had episodes of nausea and vomiting after carboprost i.m. in LSCS. So, our aim was just to compare efficacy of both these antiemetic drugs to prevent nausea and vomiting after carboprost. Effect of addition of dexamethasone to ondansetron in the control of postoperative nausea and vomiting (PONV) has been studied before [3, 4, 5] but we could not find any study in the literature that investigated the efficacy of this combination for the control of post-delivery PONV after use of carboprost. In this study, we aimed to compare the antiemetic efficacy of ondansetron and dexamethasone combination with that of the single use of ondansetron to decrease the incidence of PONV during CS under spinal anaesthesia. Individual RCTs have found that dexamethasone and ondansetron are equally effective in PONV prophylaxis after laparoscopic surgeries. However, small sample size was the most important limitation of the RCTs.

Abouleish et al[6]. found that use of 4 mg ondansetron during CS decreased the occurrence of the emetic symptoms significantly when compared with the placebo (%36 vs. %58)Alghanem et al [7] reported that ondansetron is less effective in preventing nausea in comparison of dexamethasone in endoscopic surgeries in the 0–4 h period after surgery. However, their result did not reach statistical significance probably because of small sample sizeOn the contrary Gautam et al. [8] found that dexamethasone is less effective in preventing early vomiting when compared with dexamethasone in laparoscopic cholecystectomy cases. D'Souza et al. compared dexamethasone with ondansetron for the prevention of PONV after laparoscopic gynecologic surgery and found that dexamethasone decreased the incidence of PONV and use of single dose of dexamethasone was safe, had a lesser cost and could be alternative to single dose ondansetron in this patient population[9] Longer onset of action of dexamethasone may result in relative less effectiveness in preventing early PONV. Subramaniam et al[10]found that ondansetron is more effective in preventing early PONV and dexamethasone is more effective in preventing late PONV after strabismus surgery. These findings have not been reflected in our analysis because we believe that PONV after carboprost administration during caesarean is caused by many factors such as prostaglandin release and stimulation of smooth muscle of t gastrointestinal tract. This activity may produce vomiting or diarrhea or boththose may not be fully controlled by any single prophylactic drug.Although long term administrations of corticosteroids are associated with side effects, brief administration (24-48 hours), with even high dose corticosteroid treatment, side effects have been rare.Use of single dose dexamethasone is free from significant side effects including delayed wound healing [11]. Moreover, it may decrease postoperative pain after laparoscopic cholecystectomy [12].

Glucocorticoidsused primarily as anti-allergic and anti-inflammatory drugs, are also effective, alone or combined with other antiemetic, for preventing nausea and vomiting [1]. Dexamethasone has been suggested as a first-line drug for preventing low-level emetogenic chemotherapyand radiotherapy-induced nausea and vomiting, and in patients with only one or two risks for postoperative nausea and vomiting (PONV). Dexamethasone combined with 5-HT_3 or tachykinin NK_1 antagonists is also suggested for higher-level emetogenic chemotherapy and radiotherapy and for patients at high risk for PONV[13]. Glucocorticoids may act via the following mechanisms: (1) anti-inflammatory effect; (2) direct central action at the solitary tract nucleus, (3) interaction with the neurotransmitter serotonin, and receptor proteins tachykinin NK_1 and NK_2, alpha-adrenaline, etc.; (4) maintaining the normal physiological functions of organs and systems; (5) regulation of the hypothalamic-pituitary-adrenal axis; and (6) reducing pain and the concomitant use of opioids, which in turn reduces opioid-related nausea and vomiting[14]

A meta-analysis to assess the efficacy of dexamethasone in reducing PONV showed that a single IV dose of dexamethasone 5 to 10 mg was effective in reducing PONV in women receiving neuraxial morphine for cesarean delivery or abdominal hysterectomy[15]. Additionally, the Society for Ambulatory Anesthesia guidelines recommended 4-5 mg dexamethasone IV for prevention of PONV [16]Mckenczie et a[17]studied ondansetron and combination of ondansetron with dexamethasone in women undergoing major gynecological surgeries and the results showed that the combination is more effective similarly in our study we found we found that incidence of post op nausea and vomiting is significantly lower in the OD group than in O group(43%)Vs(59%) p value of 0.036 in 0-6 hrs. and also overall in 0-24 hours 59(63%) Vs 45(45%) p value of 0.016. The most frequently reported adverse events of 5-HT3 receptor antagonists are dizziness and headache. Adverse events observed in our study were similar in both the groups. Our study demonstrates dexamethasone in combination with ondansetron in comparison to ondansetron significantly decreases the incidence of nausea and vomiting. The incidence of rescue antiemetic used was significantly lower in the OD group than in the D group during the 0-6 hours after the operation (13 vs. 24%) (P = 0.043).

V. Conclusion

We conclude that combination of dexamethasone with ondansetron is quite effective in controlling PONV in patients of LSCS under spinal anesthesia who are required to be ad mistered Carboprost. It also reduces incidence of nausea in first 24 hours post operatively and also frequency of giving rescue antiemetic is decreased.As the drug is freely available, economical and a single dose is not associated with any side effects, this combination can be used safely

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*Roshni Abichandani MS. "Comparison of Ondansetron with combination of ondansetron and dexamethasone for prevention of nausea and vomiting after Carboprost in LSCS patients under spinal anesthesia." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.9 (2017): 72-76