Comparison Between Cyclizine and Dexamethasone for Prevention of Nausea and Vomiting after Intrathecal Morphine in Patients Undergoing Cesarean Section

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Abstract:

Background: Postoperative nausea and vomiting (PONV) are frequent side effects of intrathecal morphine in patients undergoing cesarean section (CS). The prophylactic administration of combination antiemetic drugs is well established in modern anesthetic practice for the prevention of PONV in adult patients.

Methods: One hundred sixty uncomplicated term pregnant patients scheduled for elective cesarean section under spinal anesthesia were divided into two equal groups. The patients in both groups were given a subarachnoid block (2-3 mL hyperbaric bupivacaine plus 200 µg of morphine). After clamping the umbilical cord, 10 mg metoclopramide amp was added to the IV fluid in both groups. Then, the first group received 8 mg IV dexamethasone, and the second group received 50 mg IV cyclizine. The primary outcome was the number of patients who experienced PONV during the first postoperative 24 hours, and the second outcome was the side effects of the given drugs.

Results: The incidence of PONV was 25% in the dexamethasone group and 11% in the cyclizine group, with a significant difference between both groups ($p < 0.05$).

Conclusion: Combined with metoclopramide, cyclizine may be a good choice for prophylaxis against PONV in elective CS receiving intrathecal morphine.

Keywords: Postoperative nausea and vomiting, metoclopramide, cyclizine.

Introduction:

Postoperative nausea and vomiting are frequently seen in patients undergoing cesarean section (CS) under neuraxial anesthesia, especially with intrathecal morphine,[1,2]. Although the administration of intrathecal morphine provides long-lasting analgesia, it is associated with a dose-dependent increase in the incidence of PONV compared with a non-morphine spinal anesthesia.[3] Postoperative nausea and vomiting (PONV) is any nausea, retching, or vomiting occurring in patients during the first 24–48 h after surgery.[4] PONV is one of the most common causes of patients' dissatisfaction after anesthesia.[1]The goal of PONV prophylaxis is to decrease the incidence of PONV and thus the patient's distress and hospital stay.[5]

Two key areas are thought to be responsible for the vomiting reflex: the chemoreceptor trigger zone (CTZ) and the 'vomiting centre'. There are five main receptors implicated in nausea and vomiting. These are dopaminergic (D_2), histaminergic (H_1), 5-hydroxytriptamine or 5-HT_3 (serotonin), muscarinic (M_1), and neurokinin NK_1 (substance P).[6] The multifactorial etiology of PONV may necessitate increased interest in using a combination or multimodal therapies that include at least 2 interventions. [7]

Metoclopramide is an inexpensive drug that has multiple sites of action. It is a

prokinetic drug that increases the lower esophageal sphincter tone. It also has an anti-dopaminergic action on the chemoreceptor trigger zone and, at higher doses, has an anti-serotonergic activity.[8] The 10 mg dose, although it crosses the placental barrier, is considered safe in the parturient and the neonate. [9, 10]

Dexamethasone is a synthetic long-acting glucocorticoid. The mechanism of the antiemetic effect of dexamethasone is still not exactly known. The proposed mechanism may be due to the ability of dexamethasone to deplete γ-amino-butyric acid stores, reduce the blood-brain barrier's permeability to emetic toxins, and inhibit central prostaglandin synthesis, brainstem enkephalin release, and serotonin synthesis and release.[11]

Cyclizine is a piperazine derivative anti-histamine (H1 antagonist) with some anti-muscarinic properties. It is used in the prevention and treatment of nausea and vomiting.[12] Cyclizine is a cheap antiemetic with verifiable efficacy (binding to two different receptors involved in the pathogenesis of PONV) and a good adverse effect profile.[13]

Patients and Methods

This prospective, double-blinded, randomized study was carried out in Assiut University Hospital, from January 2021 to January 2022, after approval by the local research ethics committee of Assiut Faculty of Medicine, Egypt. The study protocol was registered with ClinicalTrials.gov (ID: NCT03931135). Informed consent was taken from each patient. One hundred sixty term pregnant patients, aged 18 – 40 years, scheduled for elective cesarean section under spinal anesthesia were included in the study. Excluded from the study were patients with a known allergy to the study drugs; significant cardiac, respiratory, renal, neurological, or hepatic disease; coagulation disorders; BMI > 30 kg/m^2; diabetes mellitus; any other gastrointestinal illness, hyperemesis gravidarum, or who had been administered antiemetic medication in the previous 24 hours before the operation.

All patients were instructed on the day before surgery about the study protocol and given omeprazole 40 mg at midnight. The patients in both groups were hydrated with 0.5 liter of Ringer's Lactate solution before administration of the subarachnoid block. All patients received an intrathecal injection of 0.5% (2-3 ml) hyperbaric bupivacaine in addition to 200 μg of morphine in the sitting position, then turned to a supine position with left uterine displacement. Oxygen 5L/min was administered to all patients via a face mask. The anesthetic technique was uniform for all patients. A metoclopramide 10 mg amp was added to the infusion fluid after clamping the umbilical cord in both groups.

The patients were divided randomly (by computer-generated program) into two groups.

1- The first group included 80 patients who received 8 mg IV dexamethasone after clamping of the umbilical cord (diluted in 100 mL dextrose 5% and given over 10 minutes).
2- The second group included 80 patients who received 50 mg IV cyclizine (Emetrex-Amoun) after clamping of the umbilical cord (diluted in 100 mL dextrose 5% and given over 10 minutes). To facilitate the double-blinding method, the study drugs were prepared and given by the anesthetists who were not involved in the study.

The primary outcome measure was the number of patients who experienced PONV during the first postoperative 24 hours.

PONV: using a 4-point rating scale for nausea and vomiting (1 no nausea or vomiting, 2 mild nausea, 3 severe nausea, and 4 vomiting) [14]

Rescue treatment of PONV is ondansetron 4mg IV (the rescue drug should be from a different class than those used for prophylaxis 5).

Secondary outcome measures included the side effects of the given drugs, such as tachycardia and dry mouth (mild=on direct question, severe=direct complaint), and the number of patients who received rescue treatment during the first postoperative 24 hours.

All patients were visited by the investigator and the responsible nurse 4 hours postoperatively and after 24 hours to confirm the data taken by the nurses.

Statistical Analysis:

Sample size was determined prospectively, with 80 patients per treatment group. A difference of 20% in the incidence of postoperative nausea and vomiting among treatments could be determined with a statistical power of 80% (B=0.2) and statistical significance of 0.05.

All statistical calculations were done using SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 22. Quantitative data were statistically described in terms of mean ± SD. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. *Mann-Whitney U* was used to compare both groups' quantitative variables because the data were normally distributed. For comparing categorical data, *the chi-square ($\chi 2$) test* was performed. *An exact test was used when the expected frequency wa*s less than 5. P-value is always 2-tailed and set at a 0.05 level.

Results:

Table (1): Demographic data in both groups

Item	Dexamethasone (n=80)	Cyclizine (n=80)	*P* value
Age (ys)	28.30±5.64	26.92±5.61	0.124
Weight (kg)	74.57±8.36	72.60±7.69	0.122
Height (cm)	163.29±5.71	161.69±5.74	0.079

Values are expressed as mean ± SD, numbers. *P* value non-significant > 0.05.

The heart rate at the end of the operation (HRe) was statistically higher in the cyclizine group (*P*<0.05), as shown in Table 2.

Table (2): Hemodynamic parameters in both groups

Item		Dexamethasone (n=80)	Cyclizine (n=80)	*P* value
HR	P	78.56±8.10	80.25±8.10	0.260
	E	74.68±5.63	77.63±5.60	0.004*
	4	73.93±8.25	75.51±10.02	0.347
SBP	P	129±8.65	126±8.80	0.188
	E	121±6.86	119±6.61	0.098
	4	118±7.09	116±8.46	0.236
DBP	P	78±5.66	77±6.93	0.263
	E	74±5.17	72±5.57	0.099
	4	73±5.66	71±6.40	0.202

Data are expressed as mean (± SD), * *P* < 0.05 significant, *P* > 0.05 non-significant. **HR:** heart rate, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure. ***P:*** preoperative, E: end of surgery, **4:** after 4 hours postoperative

The incidence of postoperative nausea in the dexamethasone group was 25% and in the cyclizine group was 11.3% (P < 0.05). The incidence of postoperative vomiting was 10% and 2.5% (*P* < 0.05) in the dexamethasone and cyclizine groups, respectively (**Table 3, Figure 1**).

Table (3): Postoperative incidence of nausea (with its severity) and vomiting.

Item	Dexamethasone (n=80)	Cyclizine (n=80)	*P* value
Free of N&V (%)	55 (68.75)	67 (83.75)	0.026*
Nausea, n (%)	25 (31.25)	13 (16.25)	0.026*
Nausea severity, n (%)			
- Mild	13 (52)	9 (69.2)	0.362
- Severe	12 (48)	4 (30.8)	0.035*
Vomiting, n (%)	10 (12.5)	3 (3.75)	0.043*

Values are expressed as a number (n) and percentage (%)

* *P* < 0.05 significant, *P* > 0.05 non significant. N&V nausea and vomiting.

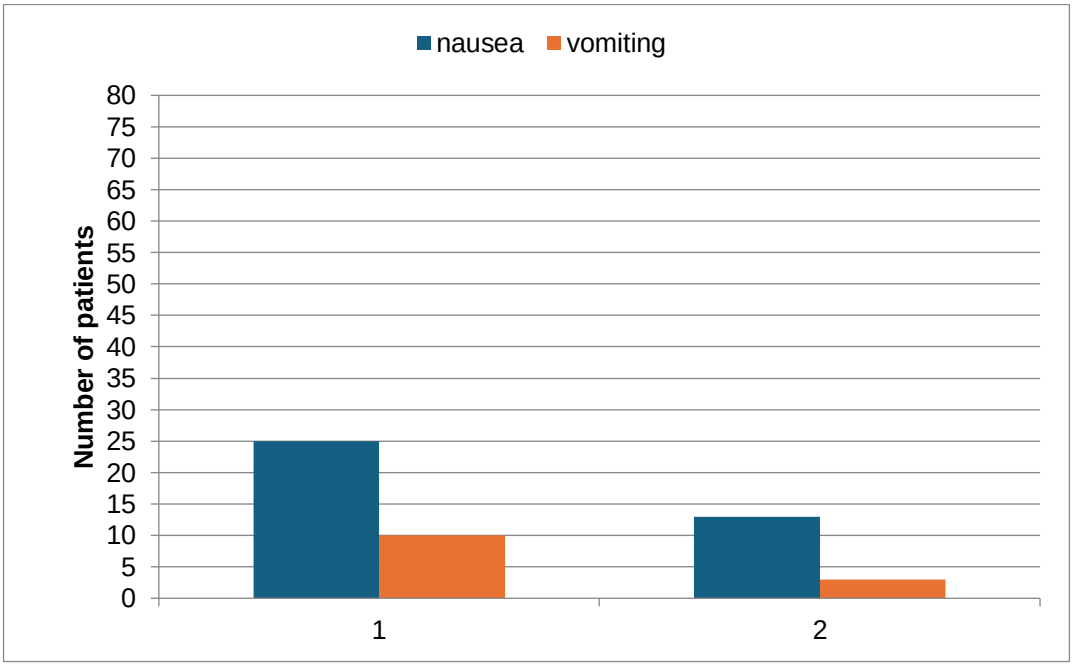

Figure (1): 1-dexamethasone group, 2- cyclizine group

The incidence of mild dry mouth was 7.5% in the cyclizine group ($P < 0.05$), and the number of patients who received rescue antiemetic drug was higher ($P < 0.05$) in the dexamethasone group (Table 4).

Table (4): Side effects of the given drugs and the number of patients who received rescue treatment

Item	Dexamethasone (n=80)	Cyclizine (n=80)	*P* value
Dry mouth, n (%)			
- Mild	1(1.25)	7 (8.75)	0.032*
- Severe	0	0	
Rescue treatment	7(8.75)	1(1.25)	0.032*

Values are expressed as a number (percentage)
* $P < 0.05$ significant

Discussion

Intrathecal administration of morphine has been associated with a frequent incidence of postoperative nausea and vomiting (PONV).15 Postoperative nausea and vomiting is a common, disturbing postoperative complication that has an important impact on patient outcome.[1]
The rate of PONV (in patients without prophylactic treatment) ranges from 23% to 79%.16.

As the prevention strategy through prophylactic administration of antiemetic drugs is better and more effective than giving therapy after the occurrence of nausea and vomiting,1 the use of combination therapy for the prevention of PONV in adult patients is well established in modern anesthesia practice[5]. We use two drugs for the prevention of PONV in both groups.

Our results have shown a statistically significant difference in the incidence of PONV with the administration of combination therapy using metoclopramide and cyclizine (MC) when compared with metoclopramide and dexamethasone (MD) after elective uncomplicated cesarean delivery under spinal anesthesia with bupivacaine and morphine. The incidence of PONV was 31.25% and 16.25% in the group MD and the group MC, respectively.

The current study revealed that, by comparing the incidence of postoperative nausea and vomiting, we found that patients who received cyclizine had significantly less incidence and severity of PONV and the need for rescue treatment than patients who received dexamethasone.

The study of Nortcliffe and his coworkers compared the antiemetic efficacy of cyclizine, dexamethasone, and placebo in controlling postoperative nausea and vomiting in 99 women who underwent elective CS under spinal anesthesia with intrathecal morphine. They reported that IV cyclizine administered immediately after elective caesarean section significantly decreased the incidence and severity of nausea and vomiting, and the need for rescue antiemetic therapy compared to dexamethasone and placebo. They concluded that cyclizine is a well-tolerated and highly effective drug in prophylaxis against PONV. [17]

A more recent prospective randomized double-blinded study done by ***Okonna et al.*** supports the use of cyclizine in preventing intraoperative nausea and vomiting in women undergoing elective cesarean section. They compared the effect of IV cyclizine with metoclopramide administered

before achieving subarachnoid block and found that the incidence of intraoperative nausea and vomiting was least in the cyclizine group. Based on this finding, the authors concluded that cyclizine (50 mg) is superior to metoclopramide in preventing intraoperative nausea and vomiting in women undergoing cesarean section under spinal anesthesia.[18]

Also, cyclizine compared to ondansetron in patients who underwent laparoscopic gynecologic surgery 19, and laparoscopic cholecystectomy 20, and both drugs were found to be equally effective in reducing the incidence of PONV.

On the other hand, the use of IV dexamethasone for prophylaxis against PONV after intrathecal morphine has conflicting evidence about its effectiveness.

Allen et al., in their meta-analysis, found that dexamethasone reduced the incidence of PONV in patients receiving neuraxial morphine for cesarean section.[11]

In another meta-analysis done by Grape and his coworkers on the effectiveness of IV dexamethasone for prophylaxis against PONV in patients who received long-acting neuraxial opioids, they stated that IV dexamethasone provides effective prophylaxis against PONV during the first 24 hours postoperatively. [21]

However, in a more recent randomized double-blind placebo-controlled study, Selzer and his colleagues found that the administration of 8 mg of dexamethasone IV before giving 0.2 mg of intrathecal morphine in patients who underwent elective cesarean section did not significantly reduce the PONV. They suggest that in the setting of intrathecal morphine, dexamethasone is ineffective as a single antiemetic agent but may act synergistically with other antiemetic agents. [2]

Cholwill et al. suggested that the type of surgery and the pathophysiology of emesis may affect the choice of drug used for the prophylaxis of PONV. So, cyclizine may be appropriate for opioid-induced PONV as it acts at histamine and muscarinic receptors. [13]

Furthermore, as cyclizine is a cheap antiemetic drug with confirmed efficacy (binding to two receptors involved in the pathogenesis of PONV) and a good adverse effect profile, it is appropriate for use in combination with other antiemetic drugs in the prophylaxis of PONV.[13]

We observed no significant difference in intraoperative hemodynamics between the groups except for heart rate. We found that patients who received cyclizine had statistically (although clinically insignificant) higher heart rate values at the end of the operation only. This finding, in addition to the mild dry mouth some patients experienced, could be explained by the fact that the vagolytic effects of cyclizine may be associated with a substantial increase in heart rate.[22]

Our study's limitation may be the use of the common doses of the antiemetic medications; however, the use of 25 mg of cyclizine (which may have lower side effects) and 20 mg of metoclopramide (which may be more effective than 10 mg) may be investigated in a future study.

Conclusion:

We concluded that cyclizine in a dose of 50 mg can be given with metoclopramide 10 mg for prophylaxis against PONV in patients who are subjected to CS under spinal anesthesia with intrathecal morphine with minimal side effects.

References:

1. Hailu S, Mekonen S, Shiferaw A. Prevention and management of postoperative nausea and vomiting after cesarean section: a systematic literature review. Ann Med Surg (Lond). 2022;75:103433.
2. Selzer A, Pryor KO, Tangel V, et al. The effect of intravenous dexamethasone on postoperative nausea and vomiting after cesarean delivery with intrathecal morphine: a

randomized-controlled trial. Can J Anaesth. 2020;67:817-26.
3. Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology. 1999;91:1919-27.
4. Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth. 2012;109(5):742-53.
5. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020;131(2):411-48.
6. Denholm L, Gallagher G. Physiology and pharmacology of nausea and vomiting. Anaesth Intensive Care Med. 2018;19(9):513-6.
7. Cao X, White PF, Ma H. An update on managing postoperative nausea and vomiting. J Anesth. 2017;31:617-26.
8. Mishriky BM, Habib AS. Metoclopramide for nausea and vomiting prophylaxis during and after caesarean delivery: a systematic review and meta-analysis. Br J Anaesth. 2012;108(3):374-83.
9. Lussos SA, Bader AM, Thornhill ML, Datta S. The antiemetic efficacy and safety of prophylactic metoclopramide for elective cesarean delivery during spinal anesthesia. Reg Anesth. 1992;17:126-30.
10. Balki M, Carvalho JC. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. Int J Obstet Anesth. 2005;14:230-41.
11. Allen TK, Jones CA, Habib AS. Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: a systematic review and meta-analysis. Anesth Analg. 2012;114(4):813-22.
12. Watts SA. A randomized double-blinded comparison of metoclopramide, ondansetron and cyclizine in day-case laparoscopy. Anaesth Intensive Care. 1996;24(5):546-51.
13. Cholwill JM, Wright W, Hobbs GJ, Curran J. Comparison of ondansetron and cyclizine to prevent nausea and vomiting after day-case gynaecological laparoscopy. Br J Anaesth. 1999;83(4):611-4.
14. Moustafa AA, Baaror AS, Abdelazim IA. Comparative study between nalbuphine and ondansetron in prevention of intrathecal morphine-induced pruritus in women undergoing cesarean section. Anesth Essays Res. 2016;10(2):238-44.
15. Koju RB, Gurung BS, Dongol Y. Prophylactic administration of ondansetron in prevention of intrathecal morphine-induced pruritus and postoperative nausea and vomiting in patients undergoing caesarean section. BMC Anesthesiol. 2015;15:18.
16. Griffiths JD, Gyte GML, Paranjothy S, et al. Interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section. Cochrane Database Syst Rev. 2012;(9):CD007579.
17. Nortcliffe SA, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine for caesarean section: comparison of cyclizine, dexamethasone and placebo. Br J Anaesth. 2003;90(5):665-70.
18. Okonna FG, Amucheazi AO, Onyekwulu FA. Preventing intraoperative nausea and vomiting during cesarean delivery under spinal anesthesia: a comparison of effects of prophylactic cyclizine, metoclopramide, and placebo. Niger J Med. 2021;30(6):653-7.
19. Grimsehl K, Whiteside JB, Mackenzie N. Comparison of cyclizine and ondansetron for the prevention of postoperative nausea and vomiting in

laparoscopic day-case gynaecological surgery. Anaesthesia. 2002;57(1):61-5.
20. Malak AM, Shameem A, Ali CA, Qureshi MA. Comparison of ondansetron, cyclizine and prochlorperazine for PONV prophylaxis in laparoscopic cholecystectomy. Anaesth Pain Intensive Care. 2017;21(4):453-7.
21. Grape S, Usmanova I, Kirkham KR, Albrecht E. Intravenous dexamethasone for prophylaxis of postoperative nausea and vomiting after administration of long-acting neuraxial opioids: a systematic review and meta-analysis. Anaesthesia. 2018;73(4):480-9.
22. Bassett KE, Schunk JE, Crouch BI. Cyclizine abuse by teenagers in Utah. Am J Emerg Med. 1996;14(5):472-4.