# A Randomized Comparison of Dimenhydrinate, Metoclopramide and Placebo for the Prevention of Nausea and Vomiting Following Intrathecal Fentanyl and Morphine in Cesarean Delivery

**Ateş Duman Assoc. Prof. MD,[1] Seza Apilioğulları Assist. Prof. MD,[2] Funda Gök MD,[3] Erdinç Sütçü MD,[4] Sema Soysal MD,[5] Harun Toy MD[5]**

[1] Selçuk Üniversitesi, Meram Tıp Fakültesi, Anesteziyoloji ve Reanimasyon AD, Konya
[2] Selçuk Üniversitesi, Diş Hekimliği Fakültesi, Cerrahi Kliniği, Anesteziyoloji ve Reanimasyon AD, Konya
[3] Faruk Sükan Doğum ve Çocuk Hastanesi, Anesteziyoloji ve Reanimasyon AD, Konya
[4] Selçuk Üniversitesi, Veterinerlik Fakültesi, Farmakoloji ve Toksikoloji AD, Konya
[5] Faruk Sükan Doğum ve Çocuk Hastanesi, Kadın Hastalıkları ve Doğum AD, Konya

## ABSTRACT

• ***Objective:*** *Intrathecal morphine for cesarean section provides excellent postoperative analgesia, however, is associated with significant nausea and vomiting. This study was designed to compare the effectiveness of prophylactic use of dimenhydrinate and metoclopramide to placebo for the prevention of nausea and vomiting following intrathecal fentanyl and morphine used for cesarean section.*

• ***Material and Method:*** *Two hundred ten patents undergoing cesarean section under spinal anesthesia were included in this double-blind and randomized study.*

*Spinal anesthesia was performed with 10 mg of hyperbaric bupivacaine combined with 20 µg fentanyl and 200 µg morphine. After clamping the umbilical cord, patients were randomly allocated to receive 50 mg dimenhydrinate intravenously (Group D), 10 mg metoclopramide (Group M) or 0.9% NaCl as placebo (Group P). The incidence of postoperative nausea or vomiting (PONV) during the first 24 postoperative hours was evaluated.*

• ***Results:*** *The postoperative incidence of PONV was significantly lower in Group D (11%) than in Group M (28%) and Group P (32%) (p=0.02). The incidence and severity of postoperative nausea were significantly lower with the use of dimenhydrinate as compared to metoclopramide and placebo group (p= 0.01).*

• ***Conclusion:*** *The prophylactic use of dimenhydrinate (50 mg intravenously) as compared either to metoclopramide (10 mg) or placebo, effectively decreased the incidence of PONV following intrathecal fentanyl and morphine for cesarean section.*

• ***Key Words:*** *Cesarean section, dimenhydrinate, fentanyl, metoclopramide, morphine.* ***Nobel Med 2010; 6(3):13-19***

## SEZARYEN AMELİYATLARI İÇİN KULLANILAN İNTRATEKAL FENTANİL VE MORFİN SONRASI GÖRÜLEN POSTOPERATİF BULANTI VE KUSMANIN ÖNLENMESİNDE DİMENHİDRİNAT, METOKLOPRAMİD VE PLASEBONUN RANDOMİZE KARŞILAŞTIRILMASI


## ÖZET

• **Amaç:** Sezaryen ameliyatları için kullanılan intratekal morfin çok iyi postoperatif analjezi sağlar ancak belirgin bulantı ve kusma ile ilişkilidir. Bu çalışma, sezaryen ameliyatları için intratekal verilen fentanil ve morfin sonrası görülen bulantı ve kusmayı önlemede, profilaktik uygulanan dimenhidrinat, metoklopramid ve plasebonun etkinliklerini kıyaslamayı amaçlamaktadır.

• **Materyal ve Metod:** Spinal anestezi yöntemiyle sezaryen ameliyatı geçirecek terminde 210 hamile, çift kör randominize çalışmaya dahil edildi. Spinal anestezi, 10 mg hiperbarik bupivakain, 20 µg fentanil ve 200 µg morfin ile gerçekleşti. Umblikal kord klemplendikten sonra hastalara randomize olarak intravenöz dimenhidrinat 50 mg (Grup D) (n=70), metoklopramid 10 mg (Group M) (n=70) ya da plasebo (%0,9 NaCl) (Grup P) (n=70) verildi. İlk 24 saatte görülen bulantı ve kusma (POBK) sıklığı değerlendirmeye alındı.

• **Bulgular:** POBK insidansı ve bulantı şiddeti Grup D'de (%11) Grup M'ye (%28) ve Grup P'ye (%32) göre anlamlı olarak düşüktü (p=0,02). Postoperatif bulantı sıklığı ve şiddeti metoklopramid ve plasebo ile kıyaslandığında dimenhidrinat kullanımı ile anlamlı olarak daha düşük bulundu (p=0,01).

• **Sonuç:** İntravenöz olarak verilen profilaktik 50 mg dimenhidrinat, 10 mg metoklopramid ve plaseboya kıyasla sezaryen ameliyatları için intratekal verilen fentanil ve morfin ile ortaya çıkan POBK insidansını belirgin olarak azaltmaktadır.



• **Anahtar Kelimeler:** Sezaryen, dimenhidrinat, fentanil, metoklopramid, morfin. **Nobel Med 2010; 6(3): 13-19**


## INTRODUCTION

Nausea and vomiting are common in parturients undergoing cesarean section performed under regional anesthesia.[1] Neuraxial opioids have been successfully used in postcesarean delivery analgesia.[2-5] However, the addition of opioids to local anesthetic solutions for spinal anesthesia is associated with an increase incidence of postoperative nausea and vomiting (PONV) which is seen in up to 67% of patients.[2] PONV can be very distressing and result in undesired consequences for patients. It can lead to medical complications and decreased patient satisfaction, and also causes an economic burden.[6-8]

Numerous antiemetic drugs have been studied for the prevention of PONV in parturients scheduled for cesarean section, and controversial outcomes have been reported.[6,9-15] Eventually no antiemetic drugs have been shown to completely prevent PONV after intrathecal opioid administration. Researches for an effective and inexpensive prophylactic drug with minimal side effects are still being continued. Dimenhydrinate is an antihistaminic drug derivated from diphenylmethane and has antiemetic properties. Metoclopramide is a benzamide derivative antiemetic drug that mediates its effect by antagonism of dopamine, and in higher doses, by antagonism of serotonin 5-HT3 receptors.[16] These two frequently used antiemetic drugs were introduced into clinical practice more than 30 years ago. They are well tolerated and are inexpensive with few known side effects.[16] To date, dimenhydrinate and metoclopramide have not been investigated for use as prophylactic drugs for intrathecal opioid induced PONV in Cesarean section. We conducted this placebo controlled study, to compare the effectiveness of dimenhydrinate and metoclopramide for the prevention of nausea and vomiting following intrathecal morphine and fentanyl combination for cesarean section.

## MATERIAL and METHOD

The study was designed as a randomized, double-blind, placebo controlled trial. This study was approved by local ethics committee of Selcuk University in accordance with the Helsinki Declaration. Written informed consent form was provided from all participants.

Two hundred and ten, non-smoking, ASA I (American Society of Anesthesiology) term parturients (>38 weeks) without pregnancy complications or major systemic diseases and without tubal ligation planning for elective Cesarean section under spinal anesthesia were enrolled in this study. Exclusion criteria were: patients for whom regional anesthesia was declined or contraindicated, patients concurrently using any antiemetic or antipsychotic medication, patients in whom NSAIDs were contraindicated, or who had a history of drug allergy, car sickness, hyperemesis gravidarum or PONV. Patients with a body weight of <50 kg or >100 kg were also excluded. →

Patients received no premedication. In the operating room, an intravenous access was established, and an infusion of 15±3 ml kg-1h-1 of a crystalloid solution was given. Standard monitoring included pulse oxymetry, electrocardiography, and non-invasive blood pressure measurement.

Spinal anesthesia was performed with a 27G atraumatic pencil point needle at the L3-L4 or L4-L5 interspace with the patient in the sitting position. An anesthetic solution containing hyperbaric bupivacaine 10 mg mixed with fentanyl 20 µg and preservative free morphine 200 µg was injected over 20 seconds. At the completion of the injection, cerebrospinal fluid was again aspirated (in a volume of 0.2-0.3 ml) and re-injected to clear the dead space of the needle. The patients were immediately placed in the supine position with a 15-degree wedge for left uterine displacement under the right hip. Episodes of hypotension (systolic arterial pressure< 90 mmHg) and bradycardia (heart rate <50 beats min-1) were treated with 5 mg ephedrine and 0.5 mg atropine as required.

After clamping of the umbilical cord, patients were randomly allocated according to computer generated random numbers to receive intravenously 50 mg dimenhydrinate (Group D) (n=70), 10 mg metoclopramide (Group M) (n=70) or 0.9% NaCl as placebo (Group P) (n=70). The study drugs as well as placebo were prepared as 10 ml solutions by using 0.9% NaCl by an anesthetist who took no further part in the study. All patients intravenously received 20 units oxytocin and 1 g cefazoline as slow infusions after placental delivery.

The patients were unaware of to which group they were allocated. Nursing staff were blinded to randomization process and selection of the drugs used in this study. During surgery the patients were sedated with increments of 0.5-1 mg.kg-1 of propofol depending on the discretion of the anesthesiologist if the patients moved because of anxiety, pain, retching or vomiting. These patients were withdrawn from the study. The primary outcome of this study was the incidence of PONV in the first 24 h after surgery. Nausea was defined as a subjectively unpleasant sensation associated with an awareness of an urge to vomit; vomiting was defined as rhythmic contractions of the abdominal muscles with or without expulsion of gastric contents from the mouth (i.e. including retching), and PONV as nausea, vomiting, or both. The severity of nausea and pruritus in the first 24 h after the spinal block was assessed on a four point scale: 0= none, 1= mild, 2= moderate, and 3= severe.[17] Intravenous ondansetron (4 mg) was given as a rescue antiemetic at the parturients' request and recorded. Pruritus was assessed on a four point categorical scale: 0= none, 1= mild, 2= moderate and; 3= severe pruritus. If treatment was needed 0.04 mg increments of naloxone was given. Sedation was assessed before the patient was discharged from the theatre, using a five point scoring scale: 0= fully awake; 1= drowsy, closed eyes; 2= asleep, but easily aroused with light tactile stimulation or simple verbal command; 3= asleep and aroused only by strong physical stimulation; 4=cannot be aroused. All assessments were carried out hourly by staff nurses trained in the scoring systems that was utilized. The maximum nausea, pruritus and sedation scores were recorded at the end of the study. Extra pyramidal symptoms such as acute dystonic and dyskinetic reactions were also recorded.

Urinary retention could not be assessed due to the routine use of indwelling urinary catheters in all patients. At the completion of surgery, all patients intravenously received twice daily 20 mg tenoxicam. Postoperative pain scores were not assessed. Respiratory depression that was defined as bradypnoeic episodes (a ventilation frequency <10 beat min-1, lasting >10 min) was treated with 0.04 mg increments of naloxone. The patients were observed for respiratory depression (at least 3 days) during their stay at the hospital.

The initial power calculation suggested that a minimum of 56 patients is needed in each of the 3 groups to demonstrate a reduction of nausea incidence from 60 to 30%, with a power of 90% and an α coefficient of 0.05. Because we planned to exclude patients who received propofol during surgery, due to propofol`s known antiemetic properties, we increased the number of patients in each group to 70.

Continuous variables are expressed as mean and standard deviation where as categorical variables are expressed as number of patients. SPSS 10.0 was used for statistical analysis. One-way ANOVA was used in the comparison of the demographic data. Categorical variables (incidence of nausea, vomiting, pruritus and requirement for rescue medication) were analyzed using chi-square analysis. p <0.05 was considered as significant.

## RESULTS

One hundred eighty two patients completed the trial: 61 in Group D, 58 in Group M, and 63 in Group P. Twenty eight patients did not complete the trial for the reasons outlined in Figure. There were no differences between the groups with respect to age, weight, height, parity, and duration of surgery (Table 1). The number of parturients with PONV, pruritus and number of patients who required rescue medication are shown in Table 2. The incidence of PONV was significantly lower in patients who received prophylactic→

**Table 1:** Demographic features and inta- and post-operative data of the patients

| | Group D (n=61) | Group M (n=58) | Group P (n=63) |
|---|---|---|---|
| Number | 61 | 58 | 63 |
| Age (yr) | 28±5 | 26±5 | 28±5 |
| Height (cm) | 160±5 | 161±5 | 159±4 |
| Weight (kg) | 73±11 | 75±10 | 77±11 |
| Parity | 2 (1-4) | 2 (1-3) | 2 (1-3) |
| Repeat CD (%) | 60 | 58 | 63 |
| Episodes of intraoperative hypotension (%) | 41 | 30 | 45 |
| Postoperative hypotension (%) | 0 | 0 | 0 |
| Duration of surgery (min) | 28±5 | 29±6 | 27±5 |

CD: Cesarean delivery. No significant difference between groups

**Table 2:** Outcomes of the groups

| | Group D (n=61) | Group M (n=58) | Group P (n=63) |
|---|---|---|---|
| Patients with PONV (n, %) | 7 (11)* | 16 (28) | 20 (32) |
| Patients with nausea (n, %) | 6 (10)* | 11 (19) | 20 (32) |
| Patients with vomiting (n, %) | 5 (8) | 13 (22) | 10 (16) |
| Severity of nausea (n) Mild/ moderate/ severe | 1/2/3* | 0/2/9 | 1/10/9 |
| Patients with pruritus (n, %) | 20 (66) | 17 (66) | 23 (67) |
| Severity of pruritus (n) Mild/ moderate/ severe | 18/0/2 | 14/0/3 | 20/1/2 |
| Rescue antiemetic (n, %) | 5 (8) | 14 (24) | 13 (21) |
| Rescue antipruritic (n, %) | 3 (5) | 3 (5) | 3 (5) |

*P<0.05

dimenhydrinate, in comparison with metoclopramide and placebo (p=0.02). The incidence and severity of postoperative nausea were significantly lower with the use of dimenhydrinate, in comparison with metoclopramide and placebo (p=0.01). Although the use of rescue medication for PONV was less in group D, it was not significant (p=0.054). The incidence, severity scores and rescue medication of pruritus were similar among the three groups. The number of patients who received ephedrine was similar among the groups. Morphine-related respiratory depression or dimenhydrinate related somnolence (sedation score >1) or metoclopramide related extra pyramidal symptoms were not observed.

## DISCUSSION

This study demonstrates the incidence of PONV in cesarean section after spinal anesthesia using 20 µg fentanyl and 200 µg morphine as 32% in the placebo group. A prophylactic single dose (50 mg) of dimenhydrinate significantly reduces PONV as compared to placebo. However, a prophylactic 10 mg metoclopramide was not effective.

Our PONV rate was lower than previously reported two studies in which the emesis rates with 200µg intrathecal morphine were 59% 2 and 67%, respectively.[11] This difference may be resultant of our strategy for prevention of both intra and postoperative nausea-vomiting including: a) exclusion of patients who receive propofol for intraoperative sedation, b) strict control of intraoperative blood pressure, c) judicious and slow administration of uterotonic agents (oxytocin) and antibiotics during both intraoperative and postoperative periods associated with nausea and vomiting, d) avoidance of vigorous movements or sudden transfer of patients either at the end of surgery or during recovery in a postoperative care unit, and e) exclusion of patients possessing a history of motion sickness.

There is a controversy regarding which is the best drug for prevention of nausea and vomiting in patients receiving intrathecal opioid. Numerous antiemetic drugs, such as cyclizine,[6] droperidol,[9,10] ondansetron,[10,14] scopolamine,[11] dexamethasone,[9] propofol,[12] nalmefene,[13] naloxone[13] and naltrexone[15] were used for the prophylaxis of PONV in parturients undergoing cesarean section. While some were found ineffective, cyclizine,[6] an antihistaminic drug, and transdermal scopolamine,[11] an anticholinergic drug, were shown to be effective with intrathecal morphine after cesarean section. Dimenhydrinate has common features with these two drugs. Both cyclizine, scopolamine and dimenhydrinate block the muscarinic-cholinergic receptors located in the vestibular pathways and vomiting centre, an action well known to prevent motion sickness.[18,19] The cardiovascular side effects of cyclizine and anticholinergic side effects of scopolamine, such as dry mouth and/ or blurry vision, are disadvantages of these drugs.[11,19]

The vomiting center receives afferents from the chemoreceptor trigger zone (CTZ), the vestibular apparatus, the cerebellum, the higher cortical, brainstem centers ,and the solitary tract nucleus. These structures are rich in dopaminergic, muscarinic, serotoninergic, histaminic and opioid receptors, and the blockage of these receptors is probably the mechanism of the antiemetic action of various drugs.[21] Dimenhydrinate is a combination of diphenhydramine and 8-chlortheophylline in equal proportions. Lin et al.[22] were the first to show that diphenhydramine provided a dose-dependent antiemetic efficacy when given intravenously→

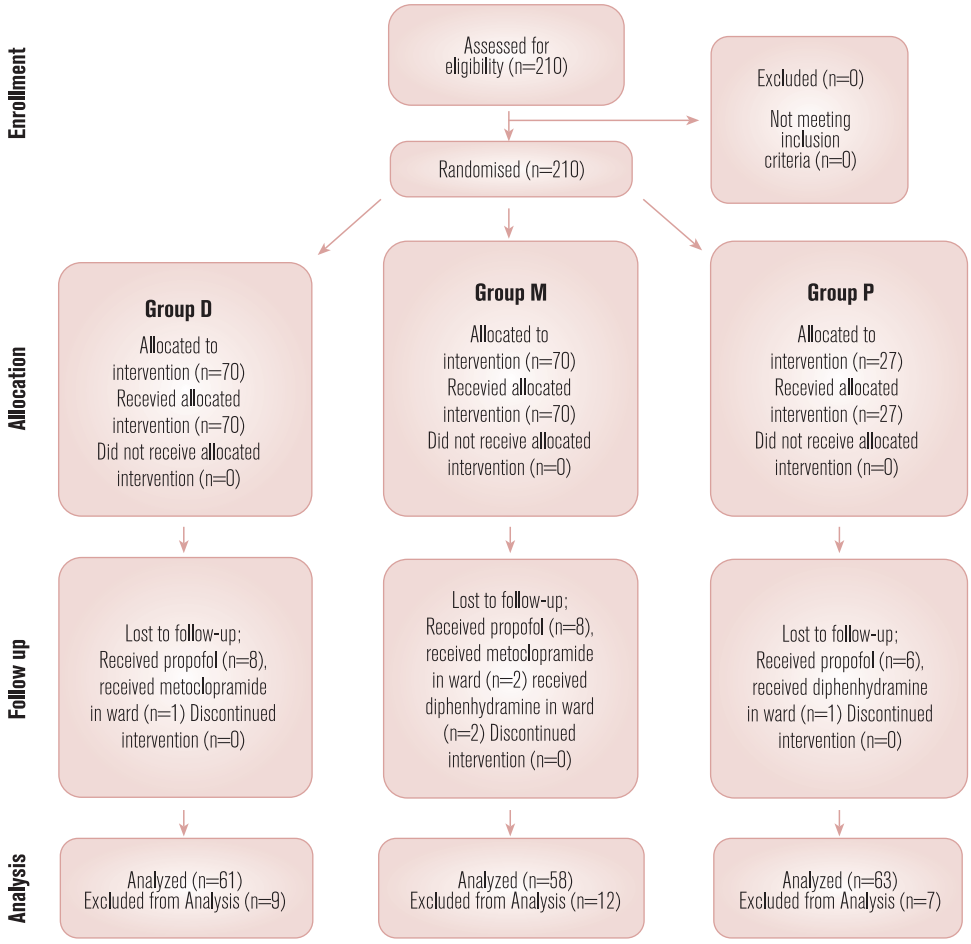


**Figure.** Flow of participants

for anesthetic induction in patients receiving intravenous morphine for postoperative analgesia. Although our findings for dimenhydrinate are similar, our administration route of morphine was different from Lin et al. Opioids are thought to induce nausea and vomiting by direct stimulation of CTZ, sensitization of the vestibular system to motion, and decreased motility of the gastrointestinal system.[23] Intrathecal morphine may spread cephalad in the cerebrospinal fluid. It reaches the CTZ 3-6 h after administration; hence, morphine is not expected to cause nausea or vomiting during intraoperative and early postoperative periods.[24] This is the reason we have chosen dimenhydrinate instead of diphenhydramine, which has a faster onset of action and elimination half life (2.5-4 h). The plasma half life of both metoclopramide and dimenhydrinate is similar (approximately 4-6 h).[16] Our negative results about metoclopramide are consistent with other studies.[25,26] Metoclopramide was previously evaluated for intrathecal 0.3 mg morphine induced PONV, and have found no significant effect after orthopedic prosthesis surgery when compared with both ondansetron and placebo.[25] It was found to be effective for the prevention of intraoperative nausea and vomiting after spinal anesthesia in Cesarean section but not in the postoperative period.[26] Our study design differs from the previous studies by means of prophylactic usage of metoclopramide for PONV.

It is a standard practice to administer a combination of fentanyl and morphine for spinal anesthesia and 20 mg tenoxicam intravenously at the end of a cesarean section in our clinic. Fentanyl is frequently added to the intrathecal local anesthetics for cesarean deliveries to improve the quality of the anesthesia. Fentanyl is a short acting opioid that stimulates the CTZ, causing vomiting, yet there are reports that fentanyl decreases the incidence of intraoperative nausea and vomiting. This has been attributed to a decrease in the somatic and visceral pain with fentanyl.[27] On the other hand, intrathecal morphine used for postoperative analgesia is related to severe PONV.[23] Non-steroidal anti-inflammatory drugs have been reported to reduce the both pain and pruritus scores[28,29] but not affect PONV30 related to spinal and epidural opioid. Our pruritus rate was 67% in the placebo group and was not different among the groups. The incidence of pruritus after intrathecal and epidural opioids reported from 0 to 100%.[23,31] Although antihistamine medicine are used for treatment of pruritus[6,23] similar to our results, a previous study→

showed that diphenhydramine was ineffective in spinal morphine induced pruritus.[32] All study groups received the same combination and the same dose of fentanyl, morphine and tenoxicam; therefore, we could expect a similar PONV and pruritus incidence in all groups.

The safety of drugs used during and after pregnancy is important. The safety of dimenhydrinate given during labor and delivery has not been well established for humans. Small amounts of diphenhydramine are excreted in breast milk. Although dimenhydrinate does not cause to adverse reactions necessitating medical attention in breast feeding, some manufacturers advise the avoidance of significant amounts of antihistamine medications in breast milk.[33] Some study protocols in cesarean section include diphenhydramine or dimenhydrinate for the treatment of pruritus or nausea.[32,34] Still, further studies on safety are needed for clinical use. Metoclopramide is useful in the treatment of deficient puerperal lactation, and it does not stimulate the pituitary lactotropes or thyrotropes of the nursing infants.[35]

One theoretical drawback for of the use of dimenhydrinate is the potential for the side effect of drowsiness and the increased arousal time after general anesthesia. In our study, all patients were fully awake with no signs of drowsiness at the end of surgery.

Delayed respiratory depression is the most feared side effect of intrathecal opioids. In the obstetric population, intrathecal morphine is associated with a very low risk of clinically significant respiratory depression. The results of a previous study showed that the incidence of severe bradypnea requiring naloxone was 1/1915 (0.052%) releated with 150µg intrathecal morphine used in cesarean section.[36] We did not encounter any episode of respiratory depression with 20µg fentanyl and 200µg morphine.

The prophylactic use of intravenous 50 mg dimenhydrinate as compared with 10 mg metoclopramide or placebo effectively decreased the postoperative incidence and severity of PONV following intrathecal fentanyl and morphine for cesarean section.

C **CORRESPONDING AUTHOR:** Ateş Duman Assoc. Prof. MD Selçuk Üniversitesi, Meram Tıp Fakültesi Anesteziyoloji ve Reanimasyon AD, Konya atesduman@hotmail.com

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