Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
October-December 2018, Volume: 10, Issue: 10, Pages: 7307-7313, DOI: http://dx.doi.org/10.19082/7307

Antiemetic effects of metoclopramide with and without dexamethasone in children with minor head trauma: a single blind randomized clinical trial

Meisam Moezzi[1], Ali Delirrooyfard[1], Hassan Motamed[1], Mohammad Kazem Mortazavi[2]

[1] Assistant Professor, Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2] Emergency Medicine Specialist, Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Type of article: Original

Abstract

Background: Trauma in the head is one of the most common childhood injuries. Children with minor head trauma are at higher risk of intracranial injury (ICI). Vomiting is one of the most common signs after minor head trauma in children, and different treatments are suggested for managing it.

Objective: To determine the antiemetic effects of dexamethasone in children with minor head trauma.

Methods: This single blind randomized clinical trial study was carried out during the period from September 2015 to August 2016 in Imam Khomeini and Golestan Hospitals in Ahvaz, Iran, on 64 children (2-8 years old) with minor head trauma (Minor head trauma was considered as GCS 14-15) who were admitted to the hospitals' emergency departments. In the intervention group, metoclopramide (0.15 mg/kg) and dexamethasone (0.15 mg/kg) were injected. In the placebo group, patients received metoclopramide (0.15 mg/kg) and placebo. Nausea severity was measured using Rhodes Index of Nausea and Vomiting. The data were analyzed using SPSS version 19. We used descriptive statistics, Chi-squared, t-test, and ANOVA for the analyses of the data. P-value of less than 0.05 was defined as the level of significance.

Results: Finally, 62 patients (mean age of 56.4 and 62% male gender) attended the study and were equally divided into intervention and placebo groups. The Rhodes Index of Nausea and Vomiting on the intervention and placebo groups was 4.9±3.73 and 7.19±3.79, respectively (p=0.021).

Conclusion: Collectively, our results indicated that dexamethasone can be used as an effective medication along with metoclopramide to control vomiting in children with minor head trauma.

Trial registration: The trial was registered at the Iranian Registry of Clinical Trials (http://www.irct.ir) with the Irct ID: IRCT2016081128944N1.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Keywords: Dexamethasone, Vomiting, Child, Craniocerebral Trauma

1. Introduction

The incidence rate of pediatric traumatic brain injury (TBI) greatly varies among countries around the world at between 47 and 280 per 100,000 children. Boys showed higher rates of TBI than girls. More than 80% of injuries are mild head injury (MHI) (Glasgow Coma Scale ≥13) (1). Historically, the definition of minor head injury was a Glasgow Coma Score (GCS) of 13-15. But recently, it has changed to a more precise definition of patients with a GCS of 15 only (2). Studies showed that children with minor head trauma are at higher risk of intracranial injury (ICI). Rotational acceleration-deceleration of the head after head trauma induces shear stress that can cause pressure on nerve fibers and lead to diffuse axonal injury (3, 4). Identification of this in patients is the main challenge in the

Corresponding author:
Ali Delirrooyfard, Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Tel: +98.9173159418, Email: adelir1982@gmail.com
Received: January 10, 2018, Accepted: April 04, 2018, Published: November 2018
iThenticate screening: March 11, 2018, English editing: May 16, 2018, Quality control: June 15, 2018
This article has been reviewed / commented by five experts
Ethics approval: IR.AJUMS.REC.1395.188 (Ahvaz Jundishapour University of Medical Sciences)

management of MHI. Currently, clinical evaluation, radiography of skull, computerized tomography (CT) scan and biochemical markers are the most diagnostic methods for MHI (5). The most recent study showed that the most common clinical presentations in patients with MHI are vomiting, headache, loss of conciseness and amnesia, and posttraumatic seizure is the least common signs (6). Preventing secondary injury is the predominant goal in the management of children with MHI. Hypoxia as a risk factor for brain injury must be identified and treated. Also, circulating volume must be considered and moreover, hyperosmolar therapy must be used to reduce ICP. However, many patients with head injury are admitted to the ED with vomiting, and antiemetic medications are widely used in these patients (7). Controversy exists about the etiology of this symptom (8). Nausea and vomiting due to severe annoyance of patients lead to an increased risk of aspiration and intracranial pressure rising (9). Metoclopramide (4-amino-5-chloro-2-methoxy-N- (2 diethylaminoethyl benzamide) is one of the oldest drugs that is widely used as an antiemetic and in the treatment of a variety of gastrointestinal disorders. The peak plasma concentrations occur approximately 1-2 hours after ingesting, and its half-life is 5-6 hours. Hepatic metabolism of metoclopramide is mediated though the cytochrome P450 CYP2D6 pathway (10). The administration of metoclopramide makes an improvement to gastrointestinal transit (10, 11). Recently, some investigators reported that dexamethasone can be prescribed to prevent postoperative nausea and vomiting (PONV) (12). In the most recent studies it has been shown that using dexamethasone in combination with other antiemetic medications is more effective than any single drug alone (13). However, the antiemetic effects of dexamethasone are not clearly understood (14). The role of dexamethasone in controlling MHI induced nausea and vomiting in children was not defined. In the current study, we aimed to determine the antiemetic effects of metoclopramide with and without dexamethasone in children with minor head trauma.

2. Material and Methods

2.1. Study design and participants

This single blind randomized clinical trial was carried out from September 2015 to August 2016 at Imam Khomeini and Golestan Hospitals (governmental educational hospitals) in Ahvaz, Iran. Imam Khomeini and Golestan Hospitals are the largest hospitals in Ahvaz, Khuzestan, Iran, and they are affiliated with Ahvaz Jundishapour University of Medical Sciences. The research population was comprised of 2 to 8 year-old patients who were admitted to the hospitals.

2.2. Selection criteria

The inclusion criteria were patients between 2 to 8 years old with minor head trauma who have presentation related to nausea and vomiting. Minor head trauma was considered as GCS 14-15. Exclusion criteria in this study were as follows: hemodynamic instability, evidence of neurologic deficit, consumption of antiemetic drugs during the eight-hour prior to admission, previous administration of intravenous fluids, radiotherapy or chemotherapy, allergy or previous adverse reaction to metoclopramide or dexamethasone. Patients who also showed extrapyramidal side effects of the drugs were excluded from the study (Figure 1).

2.3. Measurements

Nausea severity was measured using Rhodes Index of Nausea and Vomiting. Rhodes et al. introduced the Index of Nausea and Vomiting (INV) in an attempt to show the multidimensional feature of upper gastrointestinal distress. The INV has three nausea items (perceived duration, frequency, distress) and two vomiting items (amount, frequency) that are ranked on a 5-point Likert scale. The maximum possible score was 32 (none: 0, mild: 1-8, moderate: 9-16, severe: 17-24, great: 24-32) (15).

2.4. Outcomes

The primary outcome was measured by two self-reported questionnaires. The mean nausea severity was measured by Rhode's INV.

2.5. Intervention

The patients were randomly divided into two groups by block randomization method. In the treatment group, metoclopramide (0.15 mg/kg) and dexamethasone (0.15 mg/kg) were injected. In the control group, patients received metoclopramide (0.15 mg/kg) and placebo. The drugs were prepared by an independent physician in a sterilized manner. The drugs were packed in numbered, dark packs and only the main researcher knew about the drug content. So, the participants and the other colleagues were blind to the treatment group. Twenty minutes after drug administration, nausea/ vomiting and retching level was measured again. The patients who did not respond to treatment, received a rescue dose (4 mg metoclopramide).

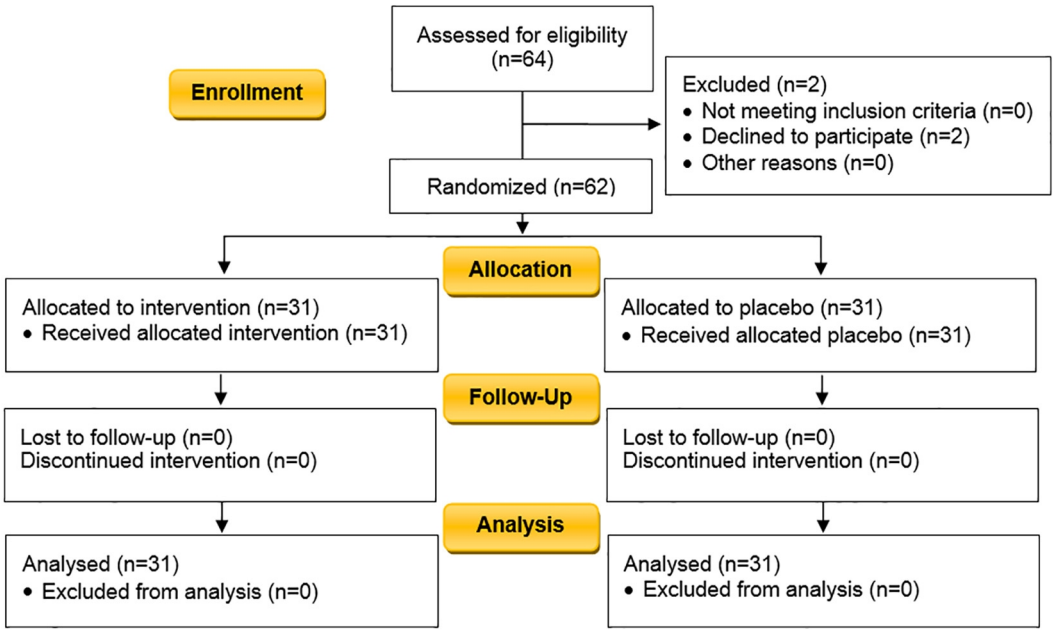

Figure 1. CONSORT 2010 Flow Diagram of the study.

2.6. Statistical analysis and sample size

By considering α=0.05 and 90% power (β=0.1), the sample size of 28 patients in each group was sufficient. It was calculated based on previous study. Ten percent dropping off was considered for the study. Finally, 64 patients were included. Nausea severity was shown as mean ± standard deviation. To compare the two groups, t-test was used. The comparison of qualitative variables such as gender between the 2 groups was done using the Chi square test. In all the analyses, $p < 0.05$ was defined as the level of significance. The data were analyzed using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA).

2.7. Research ethics

The study was approved by the ethics committee of Ahvaz Jundishapour University of Medical Sciences (IR.AJUMS.REC.1395.188). The study protocol was explained for all the participants who subsequently signed the informed consent. The study was registered at the Iranian Registry of Clinical Trials (IRCT number: IRCT2016081128944N1). The participants' information was kept confidential. All procedures were approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was assessed prior to intervention. Details that disclose the identity of the subjects under study were omitted.

3. Results

A total of 64 children with minor head trauma completed the study and two withdrew. The patients were divided into two groups of 31 (mean age 5.67±1.9 years; mean weight 21.69±6.54; 54% male). Mean age of treatment and control groups were 5.6±1.86 and 5.6±1.98 years, respectively (p=0.706). The sex distribution in the treatment group (61% male) and the control group (67.7% male) did not show any significant difference. Headache was seen in 80.6% and 70.9% of treatment and control groups, respectively, which had no significant differences. Also, drowsiness was seen in 45.16% and 32.2% of patients in treatment and control groups, respectively, the differences were not statistically significant (p=0.5). The distribution of trauma causes in the treatment group and the control group did not show any significant differences (p=0.8). The most common cause of trauma was falling down in both groups (Table1). Hemodynamic features in studied patients in both groups had no significant differences. The average score of nausea severity after administration of dexamethasone along with metoclopramide in the treatment group was 4.9±3.73. While, after administration of metoclopramide in the control group, the nausea and vomiting severity was 7.19±3.79. The nausea and vomiting average was significantly higher in the control group (p=0.021) (Table 2).

Table 1. Patients' sociodemographic characteristics.

Variables		Groups		p-value
		Treatment Group; n=31	Control Group; n=31	
Age (Mean±SD)		5.6±1.86	5.6±1.98	0.706*
Weight (Mean±SD)		22.19±6.8	20.22±6.1	0.174*
Gender; n (%)	Boy	19 (61.3)	21 (67.7)	0.791**
	Girl	12 (38.7)	10 (32.3)	
Headache; n (%)	Yes	25 (80.6)	22 (70.9)	0.68**
	No	6 (19.3)	9 (29)	
Drowsiness; n (%)	Yes	14 (45.16)	10 (32.2)	0.5**
	No	17 (54.8)	21 (67.74)	
Causes; n (%)	Accident	11 (35.5)	8 (25.8)	0.8**
	Sport injury	1 (3.2)	2 (6.5)	
	Home injury	3 (9.7)	0	
	Falling down	13 (41.9)	19 (61.3)	
	Heavy Object Head Trauma	3 (9.7)	2 (6.5)	

*Independent-samples t-test, ** Chi-Square test

Table 2. Hemodynamic features in children with minor head trauma.

Variables	Groups		p-value*
	Treatment Group; n=31	Control Group; n=31	
Systolic blood pressure (mmHg)	121.93±14	124.83±11	0.431
Diastolic blood pressure (mmHg)	74.51±6.62	80±9	0.552
Pulse rate (bpm)	89.6.24	92±6.16	0.903
O2 saturation	98.64±0.48	98.67±47	0.793
Rhode's index (After treatment)	4.9±3.73	7.19±3.79	0.021

*Independent-samples t-test

4. Discussion

Our results showed that the average score of nausea severity after administration of dexamethasone along with metoclopramide in the treatment group was significantly lower than in the placebo group. While the hemodynamic features in studied patients in both groups had no significant differences. We used Rhode's INV to assess nausea and vomiting severity. The Rhode's INV has three subscales including nausea, vomiting and retching. The maximum possible score is 32 and the cut-off level for severe symptoms is 24. It was originally invented by Rhodes (Rhodes 1984) to assess chemotherapy related nausea and vomiting (15). It is used widely in studies for evaluating nausea and vomiting severity (16). To the best of our knowledge this is the first study that has evaluated the effect of dexamethasone in children with MHI. But there are many studies that have shown effectiveness of dexamethasone in controlling nausea and vomiting induced by different clinical situations. In addition, the results of the few randomized placebo-controlled studies that have evaluated the effects of a single intravenous corticosteroid administration are conflicting, in that some studies showed a beneficial effect, while others did not. Ko-lam et al., in a randomized clinical trial (RCT), compared the prophylactic use of metoclopramide and its combination with dexamethasone in the prevention of post-operative nausea and vomiting. They showed that administration of dexamethasone along with metoclopramide had significant effect in the prevention of nausea and vomiting (17). They included 18 to 75 year-old patients and also used a different method (verbal rating scale 0-3) to evaluate nausea and vomiting severity. Moreover, the nature of conditions differed in the Ko-lam study compared with ours. Nesek et al., in another RCT compared the effect of dexamethasone, metoclopramide and a combination of them in the prevention of PONV, and reported similar findings i.e. dexamethasone and dexamethasone along with metoclopramide were more effective than metoclopramide and placebo in preventing PONV. The study was carried out on patients under laparoscopic cholecystectomy, and nausea severity was measured by VAS score (18). Moreover, Li et al., in a meta-analysis study, evaluated the seven RCTs which included 611 patients and compared the effect of administration of dexamethasone with no dexamethasone after thyroidectomy on the severity of nausea and vomiting. They indicated that prescribing dexamethasone significantly decreased the incidence and severity of

nausea and vomiting. It is worth saying that significant heterogeneity was found in the results of the included study (19). However, Wakasugi et al. assessed the efficacy of preoperative dexamethasone in the prevention of PONV in 270 patients under laparoscopic cholecystectomy. A four-point face scale was used to assess nausea severity. They found that dexamethasone had no clinical advantage for PONV (16). This inconsistency can be related with the study protocol. The Wakasugi et al. study compared dexamethasone with placebo, but our study had two groups that received metoclopramide with and without dexamethasone. Other differences are the underlying diseases (laparoscopic cholecystectomy) and the age of participants (20). Hermans et al., in another similar study, evaluated the effect of dexamethasone on nausea and vomiting in pediatric patients (2-8 years old) under tonsillectomy. The result was in line with our study and showed that the single IV injection of dexamethasone can be effective in reducing PONV (21). Moreover, some authors in Iran evaluated the antiemetic effects of dexamethasone. Kalani et al. compared the effect of ondansetron and dexamethasone in controlling nausea and vomiting in 15 to 35 year-old patients under spinal anesthesia. They only studied frequency of nausea and vomiting, and severity of them was not evaluated. Both treatments showed equal effect in reduction incidence of nausea and vomiting (22). Also, Sane et al., in another study compared IV dexamethasone, IV ondansetron, and their combination on nausea and vomiting on 90 patients under cesarean section with spinal anesthesia. They showed that intraoperative nausea was higher among patients treated with dexamethasone and lesser in patients who received their combination. But PONV was similar between the groups (23). Although the antiemetic effects of dexamethasone are well shown, the underlying mechanism of it is largely unknown (14). It has been suggested that it acts thorough direct inhibition of prostaglandins, serotonin, or endorphin production (24). The study had several limitations. Initially, we did not study dexamethasone effects solely or its administration along with metoclopramide. Moreover, it had no placebo group. A placebo group was not possible due to antiemetic intervention needed for patients. In addition, low sample size in our study can be considered as another limitation. The study was not double blind. But, the study also had some strengths. The study evaluated the dexamethasone effects on children with MHI for the first time.

5. Conclusions

Collectively, our results indicated that dexamethasone can be used as an effective medication along with metoclopramide to control vomiting in children with minor head trauma. Studying the antiemetic effect of dexamethasone in children with minor head trauma for the first time is the strength of the study. But, the low sample size and short following up are the main limitations of our study.

Acknowledgments:
We wish to thank all our colleagues in Imam Khomeini and Golestan Hospitals, Ahvaz, Iran affiliated by Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran.

Trial registration:
The trial was registered at the Iranian Registry of Clinical Trials (http://www.irct.ir) with the Irct ID: IRCT2016081128944N1.

Funding:
The authors received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References:

1) Dewan MC, Mummareddy N, Wellons JC, Bonfield CM. Epidemiology of global pediatric traumatic brain injury: qualitative review. World Neurosurgery. 2016; 91: 497-509. doi: 10.1016/j.wneu.2016.03.045. PMID: 27018009.
2) Syed AT, Lone NA, Wani MA, Bhat AS. Clinical management of patients with minor head injuries. International Journal of Health Sciences. 2007; 1(1): 131.
3) Pickering A, Harnan S, Fitzgerald P, Pandor A, Goodacre S. Clinical decision rules for children with minor head injury: a systematic review. Archives of disease in childhood. 2011; 96(5): 414-21. doi: 10.1136/adc.2010.202820. PMID: 21310894.

4) Lyttle MD, Crowe L, Oakley E, Dunning J, Babl FE. Comparing CATCH, CHALICE and PECARN clinical decision rules for paediatric head injuries. Emerg Med J. 2012; 29:785. doi: 10.1136/emermed-2011-200225. PMID: 22291431.
5) Pandor A, Goodacre S, Harnan S, Holmes M, Pickering A, Fitzgerald P, et al. Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technol Assess. 2011; 15(27): 1-202. doi: 10.3310/hta15270. PMID: 21806873, PMCID: PMC4781048.
6) Maghsoudi M, Samadzadeh M, Maghsoudi S, Isazadehfar K, Asadi T, Shahbazzadegan B. Clinical Symptoms of Minor Head Trauma and Abnormal Computed Tomography Scan. Biotechnology and Health Sciences. 2015; 2(4): e33334. doi: 10.17795/bhs-33334.
7) Wing R, James C. Pediatric head injury and concussion. Emerg Med Clin North Am. 2013; 31(3): 653-75. doi: 10.1016/j.emc.2013.05.007. PMID: 23915598.
8) Da Dalt L, Andreola B, Facchin P, Gregolin M, Vianello A, Battistella PA. Characteristics of children with vomiting after minor head trauma: a case-control study. The Journal of pediatrics. 2007; 150(3): 274-8. doi: 10.1016/j.jpeds.2006.11.060. PMID: 17307545.
9) Zamani M, Namdar B, Azizkhani R, Ahmadi O, Esmailian M. Comparing the antiemetic effects of ondansetron and metoclopramide in patients with minor head trauma. Emergency. 2015; 3(4): 137. PMID: 26495402, PMCID: PMC4608345.
10) Alonso-Campero R, Bernardo-Escudero R, de Jesús Francisco-Doce MT, Cortés-Fuentes M, Castañeda-Hernandez G, Ortiz MI. Bioequivalence Study of Metoclopramide Hydrochloride 10 mg Tablets in Healthy Male Volunteers. J Bioequiv Availab. 2011. 3(10): 222-7.
11) Magueur E, Hagege H, Attali P, Singlas E, Etienne JP, Taburet AM. Pharmacokinetics of metoclopramide in patients with liver cirrhosis. British journal of clinical pharmacology. 1991; 31(2): 185-7. doi: 10.1111/j.1365-2125.1991.tb05511.x. PMID: 2049236, PMCID: PMC1368389.
12) Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg. 2000; 90(1): 186-94. doi: 10.1097/00000539-200001000-00038. PMID: 10625002.
13) Ho CM, Wu HL, Ho ST, Wang JJ. Dexamethasone prevents postoperative nausea and vomiting: benefit versus risk. Acta Anaesthesiologica Taiwanica. 2011; 49(3): 100-4. doi: 10.1016/j.aat.2011.06.002. PMID: 21982171.
14) Chu CC, Hsing CH, Shieh JP, Chien CC, Ho CM, Wang JJ. The cellular mechanisms of the antiemetic action of dexamethasone and related glucocorticoids against vomiting. European journal of pharmacology. 2014; 722: 48-54. doi: 10.1016/j.ejphar.2013.10.008. PMID: 24184695.
15) Rhodes V, Watson P, Johnson M. Development of a reliable and valid measures of nausea and vomiting. Cancer Nursing. 1984; 7(1): 33–41. doi: 10.1097/00002820-198402000-00003. PMID: 6559094.
16) Matthews A, Haas DM, O'Mathúna DP, Dowswell T, Doyle M. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2015; (9): CD007575. doi: 10.1002/14651858.CD007575.pub4. PMID: 26348534.
17) Pongchairerks P, Junrungsee S, Chotirosniramit A, Chotirosniramit N, Chandacham K, Jirapongcharoenlap T. Metoclopramide, versus its combination with dexamethasone in the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy: a double-blind randomized controlled trial. J Med Assoc Thai. 2015; 98(3): 265-72. PMID: 25920297.
18) Nesek-Adam V, Grizelj-Stojčić E, Rašić Ž, Čala Z, Mršić V, Smiljanić A. Comparison of dexamethasone, metoclopramide, and their combination in the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Surgical endoscopy. 2007; 21(4): 607-12. doi: 10.1007/s00464-006-9122-7. PMID: 17285386.
19) Li B, Wang H. Dexamethasone reduces nausea and vomiting but not pain after thyroid surgery: a meta-analysis of randomized controlled trials. Med Sci Monit. 2014; 20: 2837-45. doi: 10.12659/MSM.891390. PMID: 25549754, PMCID: PMC4288396.
20) Wakasugi M, Tori M, Shimizu J, Kim YK, Noda T, Dono K, et al. Efficacy of preoperative dexamethasone for postoperative nausea and vomiting after laparoscopic cholecystectomy: a large‐scale, multicenter, randomized, double‐blind, placebo‐controlled trial in Japan. Journal of hepato-biliary-pancreatic sciences. 2015; 22(11): 802-9. doi: 10.1002/jhbp.285. PMID: 26288165.
21) Hermans V, De Pooter F, De Groote F, De Hert S, Van der Linden P. Effect of dexamethasone on nausea, vomiting, and pain in paediatric tonsillectomy. Br J Anaesth. 2012; 109(3): 427-31. doi: 10.1093/bja/aes249. PMID: 22879656.

22) Kalani N, Zabetian H, Sanie MS, Deylami M, Radmehr M, Sahraei R, et al. The Effect of Ondansetron and Dexamethasone on Nausea and Vomiting under Spinal Anesthesia. World J Plast Surg. 2017; 6(1): 88. PMID: 28289619, PMCID: PMC5339615.
23) Sane S, Hasanlui MV, Abbasivash R, Mahoori A, Hashemi ST, Rafiei F. Comparing the effect of intravenous dexamethasone, intravenous ondansetron, and their combination on nausea and vomiting in cesarean section with spinal anesthesia. Adv Biomed Res. 2015; 4: 230. doi: 10.4103/2277-9175.167030. PMID: 26623405, PMCID: PMC4638052.
24) Elhakim M, Ali NM, Rashed I, Riad MK, Refat M. Dexamethasone reduces postoperative vomiting and pain after pediatric tonsillectomy. Can J Anaesth. 2003; 50: 392–7. doi: 10.1007/BF03021038. PMID: 12670818.