Original Article

Anti-emetic effect of combined dexamethasone and dimenhydrinate on post-operative nausea and vomiting in patients undergoing open appendectomy

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Objective: To compare the anti-emetic effect of pre-operatively administered combination of dexamethasone and dimenhydrinate versus dimenhydrinate only on post-operative nausea and vomiting in patients undergoing open appendectomy.

Methodology: In this double-blinded randomized parallel group study, 90 patients undergoing open appendectomy were selected. Group I, received a combination of 8mg dexamethasone and 50mg dimenhydrinate pre-operatively and the group II received 50mg dimenhydrinate only. Patients and observing researcher were completely blinded to the treatment protocol given pre-operatively. The pharmacological variables of anesthesia were kept at a near constant level for all the subjects. Nausea and vomiting were assessed at 0-5 hours post-operatively.

Results: After excluding the patients with per-operatively discovered perforated appendix or post-operative histopathology report showing appendix to be non-inflamed, there were 44 patients in CDD (combined dexamethasone dimenhydrinate) group and 44 patients in D (dimenhydrinate only) group. Asymptomatic cases were observed in 45.4% of the CDD group while only 15.9% of the D group had asymptomatic cases at 0-5 hours post-operatively (p=0.006). Regarding nausea, 50% patients from CDD group and 81.8% from D group experienced some degree of post-operative nausea (p=0.002); 22.7% patients from CDD group and 54.5% from D group also experienced 1 or more than 1 episodes of vomiting during this time interval (p=0.002).

Conclusion: Pre-operative administration of a combination of 8mg intravenous dexamethasone and 50mg intravenous dimenhydrinate resulted in statistically significant lower incidence of post-operative nausea and vomiting at 0-5 hours post-operatively in patients undergoing open appendectomy. (Rawal Med J 201;43:106-110).

Key words: Dexamethasone, dimenhydrinate, acute appendicitis, open appendectomy, post-operative nausea and vomiting.

INTRODUCTION

The overall lifetime risk of acute appendicitis is 8.6% and 6.7% for males and females, respectively,[1] accounting for 17% of all the cases of an acute abdomen.[2] Post-operative complications of open appendectomy include nausea, vomiting, pain at incision and visceral sites, infectious complications, intra-peritoneal abscess formation, incisional hernia, and so forth.[3] During general anesthesia using volatile gases, overall incidence of post operative nausea and vomiting (PONV) is 20 to 30%.[26]

In recent years, dexamethasone has been increasingly recognized for its use as an anti-emetic agent on surgical floors.[4-6] It works by action on medullary bilateral nuclei tractus solitarii, inhibition of prostaglandin synthesis and stimulation of endorphins synthesis. Onset of action is relatively slow, taking 1-2 hours, and the action lasts for 24-36 hours.[7] Dimenhydrinate is histamine receptor H1 antagonist, but it also exerts its anti-emetic effects by interacting with other neurotransmitter systems like acetylcholine, serotonin, norepinephrine and dopamine. Onset of action takes 15-30 minutes and lasts for about 4-6 hours.[8-9] We chose this drug due to its relative cost-effectiveness and common availability in anesthesia setups. Common adverse effects are allergy, hallucinations, restlessness, urinary retention and uncommonly, seizures.

Multimodal antiemetic approach describes using different antiemetic agents with different mechanisms and sites of action, leading to requirement of lower doses of individual agents and preventing unwanted adverse effects. Etiology of PONV is multifactorial and it is only logical to adopt multiple drugs to tackle it.[10] Previously, only a few researches have been done for finding an effective post-operative multimodal antiemetic therapy for open appendectomy. Hypothesis was formulated that the patients receiving a combination of dexamethasone and dimenhydrinate pre-operatively will have statistically significant lower incidence of PONV as compared to patients receiving dimenhydrinate only.

METHODOLOGY

This double-blind randomized parallel group study was approved by Ethics Review Committee of Rawalpindi Medical College and Allied Hospital. The study setting was Benazir Bhutto Hospital, Rawalpindi, Pakistan and duration was March-April, 2017. Inclusion criteria were adult patients (aged 18 years or older) undergoing open appendectomy, ASA category 1, who gave written consent to the study intervention and had histopathologically proven appendicitis, post-operatively. Exclusion criteria was patients using systemic or oral steroids or immunosuppressive agents, pregnant or lactating mothers, diabetic patients, motion sickness, gastrointestinal disease, cardiac or respiratory disease or patients with a known sensitivity/allergy to dimenhydrinate. Cases in which post-operatively performed histopathology failed to document acute appendicitis and per-operatively discovered perforated appendix were excluded from the study. Guided by the incidence of PONV from comparable surgical populations and studies,[13] a sample size of 45 patients in each group was needed, given a significance of 5%, a power of 80% and a superiority margin of 5%.

Patients with acute appendicitis were assigned treatment protocol according to a computer generated randomization schedule, which listed the allocation sequences assigned to each of the two intervention groups (combined dexamethasone and dimenhydrinate group "CDD" and dimenhydrinate only group "D"). They were given the treatment by one of the investigator who administered prepared injections containing the drugs (blinded to treatment sequence), prepared by a nurse who was aware of the randomization schedule and was not part of the rest of the study. Intervention was with either 8mg of dexamethasone plus 50mg dimenhydrinate or 50mg dimenhydrinate only, both diluted to make a total of 5ml injection and labelled with an allocation sequence/code.

The pharmacological variables of anesthesia were kept at a near constant level for all the participants. As per policy of aforementioned hospital, TIVA (total intravenous anesthesia[14] was used for induction, and isoflurane and nitrous oxide were used as maintenance gases, each of them optimized at a constant level for all patients. Heart rate, blood pressure, respiratory rate, temperature, oxygen saturation, cardiac function, end tidal carbon dioxide, respiratory volumes were monitored continuously using the digital anesthesia work station.Throughout the study, the patients and investigators involved in study were blinded to the intervention assignments.

Primary outcome was POVN assessed at 0-5 hours post-operatively. Nausea was defined as a subjective feeling of an urge to vomit and measured by VAS (Visual Analogue Scale). Vomiting was described as a forceful expulsion of gastric contents into the mouth. Secondary outcome was requirement of any post-operative Rescue anti-emetic,[15] which was usually 50mg intravenous dimenhydrinate, unless contraindicated. Those patients were considered for rescue anti-emetic therapy who reported either moderate to severe nausea or had 2 or more than 2 episodes of vomiting. Asymptomatic cases were defined as those with no incidence of PONV 0-5 hours post-operatively.

RESULTS

A total of 114 patients were enrolled in the study, after getting their consent, against our required sample size of 90. Among them, post-operative histopathology report of 14 patients showed appendix to be non-inflamed, while 12 of the patients had perforated appendix discovered per-

operatively, these cases were excluded from the study, leaving 44 patients (23 females, 21 males) in CDD group and 44 in D group (20 females, 24 males), a total of 88 patients.

Asymptomatic cases were observed in 45.4% of the CDD group (20 out of 44 patients), while only 15.9% of the D group (7 out of 44 patients) had asymptomatic cases as observed 0-5 hours post-operatively (p=0.006). 50% patients of CDD group (22 out of 44) experienced nausea during the post-operative period while a statistically significant 81.8% patients of D group (36 out of 44) had nausea during this time interval (p=0.002)(Table 1).

Table 1. Comparison of nausea.

Groups	Grading (nausea)	0-5 hours post-operatively	Females	Males
CDD group (n=44)	No nausea	22 (50%)	8(36%)	14 (64%)
	Mild	17 (38.6%)	12 (70%)	5 (30%)
	Moderate	5 (11.3%)	3 (60%)	2 (40%)
	Severe	0		
D group (n=44)	No nausea	8 (18.1%)	3 (37.5%)	5 (62.5%)
	Mild	27 (61.3%)	11 (40.7%)	16 (59.3%)
	Moderate	6 (13.6%)	4 (66.6%)	2 (33.3%)
	Severe	3 (6.8%)	2 (66.6%)	1 (33.3%)

Table 2. Comparison of vomiting.

Groups	Grading (vomiting)	0-5 hours post-operatively	Females	Males
CDD group (n=44)	No vomiting	34 (77.2%)	16 (47%)	18 (53%)
	1 episode	9 (20.4%)	6 (66.6%)	3 (33.3%)
	2 episodes	1 (2.2%)	1 (100%)	0
	3 or more than 3 episodes	0		
D group (n=44)	No vomiting	20 (45.4%)	8 (40%)	12 (60%)
	1 episode	17 (38.6%)	9 (53%)	8 (47%)
	2 episodes	6 (13.6%)	2 (33.3%)	4 (66.6%)
	3 or more than 3 episodes	1 (2.2%)	1 (100%)	0

22.7% patients of CDD group (10 out of 44) experienced nausea during the post-operative period while a statistically significant 54.5% patients of D group (24 out of 44) had nausea during this time interval (p=0.002) (Table 2). Regarding the need for any rescue anti-emetic therapy, 11.4% (5 out of 44 patients) from the CDD group while 27.3% (12 out of 44 patients) within the D group had to be administered rescue anti-emetic drug, 50mg IV dimenhydrinate in single dose.

DICSUSSION

Previously, a few clinical trials have been carried out to determine the anti-emetic role of dexamethasone in patients undergoing appendectomy.[16] These studies showed a mixed response for anti-emetic effect of dexamethasone post-operatively. Also, our reference study[17] showed a statistically insignificant PONV effect of dexamethasone. This result might be in part due to the fact that their exclusion criteria did not include perforated appendix, which has a higher incidence PONV as compared to inflamed appendix only.[18] In contrast, in this double-blinded, randomized clinical trial, only those patients were taken into consideration who had histopathologically proven inflamed and per-operatively discovered non-perforated appendix. Since the per-operative risk factors like dosage of drugs used in TIVA and volume of maintenance gases can also affect the PONV, therefore, these factors were kept at a near constant level for all the patients.

The concept of pre-operatively administered multimodal anti-emetic therapy for patients undergoing open appendectomy is introduced in this study, and hypothesis was structured that patients receiving combined dexamethasone and dimenhydrinate will have statistically significant lower incidence of PONV at 0-5 hours post-operatively. As per results, there is a statistically significant (p=0.006) difference in the asymptomatic cases between the CDD and D groups, thereby more patients in the CDD group had complete response measured at 0-5 hours post-operatively. This supported the anti-emetic role of dexamethasone and the concept of multimodal anti-emetic therapy, which proves that if two anti-emetics with different mechanisms and sites of actions, are given simultaneously, their combined action is significantly better as compared to one of the anti-emetic agent given alone and have a lesser adverse effects profile.

Regarding the incidence of nausea and vomiting, there was also a statistically significant difference upon comparison between the two groups, thereby further potentiating the notion that dexamethasone,

either alone, or in comparison with another anti-emetic agent, has a definitive anti-emetic role. We also took into account the gender distribution of PONV among the two groups. As expected[19] females were the major victims of moderate to severe PONV. This result may prove the notion that the female gender is, in itself, an independent risk factor for PONV.

This study only focused on open appendectomy procedures. Before making the multimodal anti-emetic regimen of dexamethasone and dimenhydrinate as a standard protocol in acute appendicitis, its efficacy and adverse effect profile should also be extensively investigated in the emerging laparoscopic appendectomy[20] procedures as well.

CONCLUSION

Pre-operative administration of a combination of 8mg IV dexamethasone and 50mg IV dimenhydrinate resulted in statistically significant lower incidence of post-operative nausea and vomiting in patients undergoing open appendectomy.

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