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Gabapentin and Prevention of Post-Operative Nausea and Vomiting (PONV)

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Abstract **Original Research Article**

Background: Postoperative nausea and vomiting (PONV) is a major complication after abdominal surgery. Gabapentine has versatile role in case of convulsion and neuropathic pain management. Recently it has been used for the prevention of PONV. ***Objective:*** To evaluate the action of prophylactic gabapentin in preventing PONV in Laparoscopic cholecystectomy patients. ***Methods:*** It was a randomized placebo-controlled, double-blind study conducted in the Department of Anesthesiology, Dhaka Medical College Hospital from August 2016 to January 2017. A total number of 220 patients were selected by purposive sampling. They were divided into 2 Each group 110. After obtaining a detailed history, General physical and systemic examinations were done for all enrolled patients, after obtaining a detailed history and relevant investigations were done. The results were tested by chi-square test to see their level of significance level at <0.05. ***Results:*** Of the 220 patients, 51.81% male and 48.18% were female patients respectively belonged to the study group whereas 55.45% and 44.54% were male and female patients. The mean age of the study group and control group were 45.31±13.63 and 47.03±15.51. The mean BMI in both groups was 23.69±3.12 and 24.17±4.73. The mean arterial pressure in both groups was 96.73±8.19 and 93.35±6.37. The total mean of intravenous fluid study and control group were 1233.7±29.5 and 1139.83±55.69. The total duration of surgery in the study group was 51.77±3.95 and the control group was 46.63±7.89. From the point of view of PONV, gabapentine has shown significantly higher efficacy than placebo (P=<0.05). Out of 53 patients affected by PONV in the study group 13(24.52%), 30(56.60%), and 10(18.86%) patients were categorized as mild-moderate and severe PONV whereas 29(26.36%) 71(64.54%) and 20(18.18%) were upholder as their counterpart in the control group. In severe grade, there was no statistically significant difference found between the groups but in mild (p=0.039) and moderate category (p=0.043) statistically significant differences were observed between the groups. ***Conclusion:*** This study revealed a significantly higher efficacy of prophylactic gabapentin in reducing post-operative nausea and vomiting in the case of laparoscopic cholecystectomy. Regarding the question of the severity of PONV, this study has shown a mixed pattern of results. It requires further study to clarify the mechanism of influencing the severity of PONV.

Key word: PONV, Study group, Patients, Control group, Gabapentine, Total.

INTRODUCTION

Post-operative nausea and vomiting (PONV) is the fifth commonest general complication of major abdominal surgery. It accounts for at least 25-30% of all cases [1]. As many as 70-80% of patients are always at risk of postoperative nausea and vomiting (PONV) [2].

Despite being self-limiting, it is associated with substantial distress to patients in the recovery room. From the very beginning, if this post-operative complication can be acknowledged, a substantial reduction in health care cost can be possible by reducing the recovery room stay of patients [3]. There are multiple factors that can induce postoperative nausea and vomiting (PONV) in the case of major abdominal surgery. It is associated with substantial distress to patients in the early postoperative period, despite being self-limiting. Its prevention and/or treatment significantly improve patient satisfaction and quality of life [4]. Post-operative nausea and vomiting (PONV) prevention can lead to a substantial reduction in health care costs by reducing the duration of the postanaesthesia care unit (PACU) stay [3]. It is estimated that each episode of emesis delays discharge from the PACU by approximately 20 min.5 Furthermore, serious complications, including aspiration, wound dehiscence, oesophageal rupture, retinal detachment, and subcutaneous emphysema, related to postoperative nausea and vomiting can be prevented. The general incidence of postoperative nausea and vomiting (PONV) ranges from 25% to 30%,6 and in some subsets of high-risk patients it can be as high as 80% [7], even after preventive pharmacotherapy. The pharmacotherapies used in the prevention/ management of postoperative nausea and vomiting (PONV) include 5-HT3, dopaminergic, histaminic, and NK1 antagonists. However, the need for cheaper and more effective therapies cannot be disputed. The etiology of postoperative nausea and vomiting (PONV) is complex and dependent on a variety of factors, including the technique of anesthesia, patient demographics, and type and site of surgery [8]. With the effective reduction of frequency of postoperative nausea and vomiting (PONV) early shifting of patients from recovery room to ward is possible. That can also reduce medical costs significantly. In this regard, Gabapentin may be an effective choice. Gabapentin is a Ɣ-aminobutyric acid (GABA) analogue. In 1994, it was first approved by the Food and Drug Administration of USA for use as an adjunctive medication to control partial seizures (effective when it is added with other antiepileptic drugs) [9]. In 2002, an indication of using this drug was added. This new indication was the treatment of post-herpetic neuralgia (neuropathic pain following shingles). Nerve-related pain and other painful neuropathies [9]. Its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels but its exact mechanism of action is unknown. It is thought to bind to the α28 subunit (1 and 2)10 of voltage-dependent calcium channel in the central nervous system [11]. So it has been already used as an anticonvulsant and analgesic purpose. Its clinical use is gaining popularity day by day due to its safety profile, minimal drug interactions, pharmacokinetics (good oral bioavailability and renal elimination), and relatively flat dose-response relationship with respect to safety and efficacy [12]. Gabapentin is available only as oral preparations and its absorption is dose-dependent due to a saturable L-amino acid transport mechanism in the intestine [13]. Mean maximum plasma concentrations are attained in 2-3hr. after a single oral dose of 300mg. The oral bioavailability of a single 300mg oral dose of gabapentin is 60% and varies inversely with dose. It does not bind to plasma proteins14 and is not metabolized in humans. The elimination rate constant, plasma clearance, and renal clearance are linearly related to creatinine clearance. In patients with normal renal function the elimination half-life of gabapentin, when administered as monotherapy, is between 4.8 and 8.7 hr.15 Interestingly, in an open clinical study the anti-nausea effect of gabapentin in chemotherapy-induced acute (within 24 hours) and delayed onset (days 2-5) nausea and vomiting in breast cancer.16 Gabapentin could reduce vomiting and post-operative nausea and successfully in the case of laparoscopic cholecystectomy [8]. Tachykinin neurotransmitter activity changes in response to gabapentin, which may be the possible mechanism. Therefore, reduction after surgery and chemotherapy the effects of tachykinin seem to be the mechanism common leading to nausea [17]. Laparoscopic cholecystectomies are a common operation usually performed in as many as 42-72% of patients [18]. This study will try to study the anti-emetic effect of prophylactic gabapentin in patients who will undergo laparoscopic cholecystectomy.

OBJECTIVE

General Objective

To study the action of prophylactic gabapentin in preventing post-operative nausea and vomiting in laparoscopic cholecystectomy patients

Specific Objective

- To assess the need of adjunct drug like metochlopromide in case of gabapentin prophylaxis.
- To observe the frequency of post-operative nausea and vomiting in laparoscopic cholecystectomy.
- To find out the period of remaining patients in recovery.

MATERIALS AND METHODS

This was a randomized placebo-controlled, double blind study conducted among the patients who will undergo Laparoscopic Cholecystectomy under Department of Anesthesia in Dhaka Medical College Hospital, Dhaka, from August, 2016 to January, 2017. A total number of 220 patients were selected. They were divided into 2 groups by lottery method. Each group contained 110. After obtaining a detailed history, general physical and systemic examination were done for all enrolled patients and they were subjected to do relevant investigations. The data were collected by the

active participation of the patient's interview by the preformed proforma of data collection sheet and then data were gathered, decorated, tabulated after data cleaning and edition. Then the results were found and they were tested by chi-square test (qualitative data) to see their level of significance i, e p-value which was set as the cut off level at <0.05. So if p-value is >0.05 the results are not significant.

Table-1: Distribution of patients according to demographic profile (N=220)

Demographic Characteristics	Study group (n=110)	Control group (n=110)	p- Value
Mean Age (In years)	45.31± 13.63	47.03±15.51	0.750
Gender			
Male	57(51.81)	61(55.45)	
Female	53(48.18)	49(44.54)	0.490
BMI	23-69±3.12	24.17±4.73	0.970
MAP, mmHg	96.73±8.19	93.35±6.37	0.830
IV fluid intake, mL	1233.7±29.5	1139.83±55.69	0.290
Duration of Surgery, min	51.77±3.95	46.63±7.89	0.630

Table-1shows that of the 220 patients participated in this study , 51.81% and 48.18% male and female patients respectively belonged to study group whereas 55.45% and 44.54% male and female patients respectively participated in the control group , The mean age of study group and control group participants were 45.31±13.63 years and 47.03±15.51 years respectively. The mean BMI in both groups were 23.69±3.12 and 24.17±4.73 respectively, likely, the mean arterial pressure in both groups were 96.73±8.19 and 93.35±6.37 respectively. Total mean of intravenous fluid taken by study and control group participants were 1233.7±29.5 and 1139.83±55.69 ml respectively .total duration of surgery in study group was 51.77±3.95 min and in control group was 46.63±7.89 min respectively.

Table-2: Distribution of patients according to outcome of usage of drugs (N= 220)

	Study group (n=110)	Control group (n=110)	p- Value
Nausea	29	71	0.0001^S
Vomiting	24	39	0.003^S
Antiemetic requirement	26	69	0.001^S
Postoperative Hospital stay (d, median)	2	3	0.033^S
Post-operative hospital admission (d, median)	1(1-3)	2(1-3)	0.003^S

Table–2 shows that from the point of view of PONV, antiemetic requirements, Postoperative hospital stay and postoperative hospital readmission gabapentine has shown significant higher efficacy than placebo (P= < 0.05).

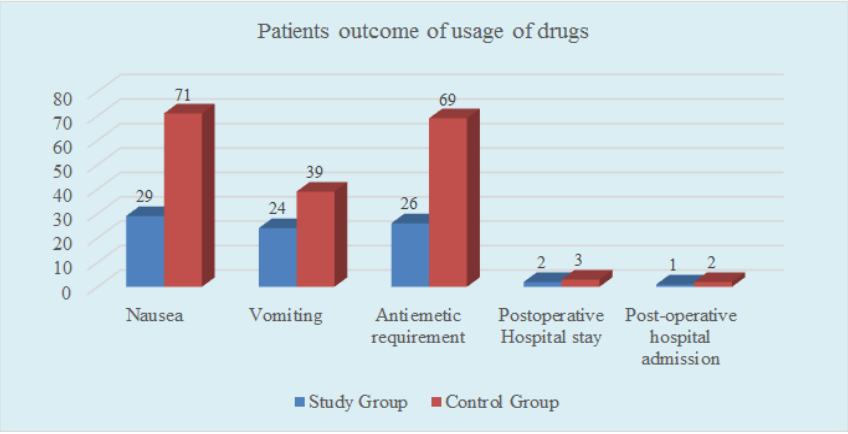

Fig-I: Distribution of patients according to outcome of usage of drugs (N=220)

Table-3: Distribution of patients according to drugs adverse effect (N= 220)

Adverse Effect	Study group (n=110)	Control group (n=110)
Drowsiness	3 (2.72)	1(0.9)
Itching	0(0.0)	3(2.72)
Light headedness	3(2.72)	0(0.0)
Feeling of 'high'	1(0.9)	0.0
Lack of concentration	2(1.81)	0.0
Headache	2(1.81)	0.0

Table-3 showed that drowsiness and light headedness were the commonest adverse effect in study group whereas itching was their counter past in control group.

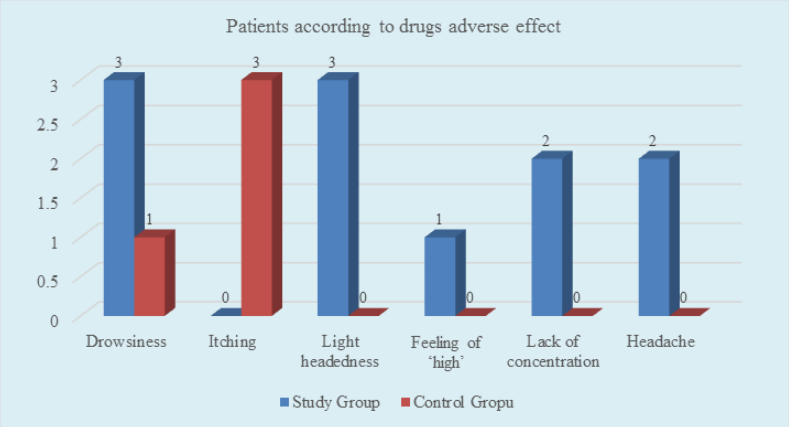

Fig-II: Distribution of patients according to drugs adverse effect (N= 220)

Table–4: Distribution of patients grade of Post-operative nausea and vomiting (PONV) (N=181)

PONV	Study group (n=53)	Control group (n=110)	p-Value
Mild	13(24.52)	29(26.36)	0.039[S]
Moderate	30(56.6)	71(64.54)	0.043[S]
Severe	10(18.86)	20(18.18)	0.075

Table-4 showed that out of 53 patients affected by Post-operative nausea and vomiting (PONV) in study group 13(24.52%), 30(56.60%) and 10(18.86%) patients were categorized as mild moderate and severe PONV whereas 29(26.36%) 71(64.54%) and 20(18.18%) were upholder as their counterpart in control group. In severe grade, these was no statistical significant difference found between the groups but in mild (p=0.039) and moderate category (p=0.043) statistical significant differences were observed between the groups.

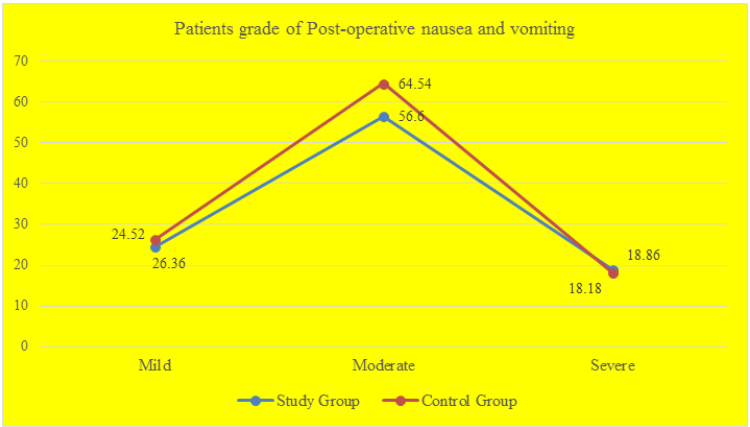

Fig-III: Distribution of patients grade of Post-operative nausea and vomiting (N= 220)

DISCUSSION

Post-operative nausea and vomiting (PONV) causative factors are complex. This postoperative complication depends upon patient, medical and surgery-related factors. General anesthesia is associated with an increased likelihood of Post-operative nausea and vomiting (PONV) by 11 times compared to other types of anesthesia and the longer the duration of anesthesia more the likelihood of Post-operative nausea and vomiting (PONV) [19]. Although some of the ways that gabapentin influences the body is known, the mechanism of postoperative nausea and vomiting (PONV) prevention by gabapentin is not yet clear. Changes in tachykinin activity or reduction in opioid usage have been proposed as mechanisms of postoperative nausea and vomiting (PONV) reduction [20]. Gabapentin is effective for reducing nausea and vomiting that is induced by chemotherapy [21]. A possible mechanism for this effect is a change in tachykinin neurotransmitter activity in response to gabapentin [22]. Therefore, tachykinin effects may be a mechanism common to nausea reduction after chemotherapy and surgery. The etiology of postoperative nausea and vomiting (PONV) after surgeries such as Laparoscopic Cholecystectomy decreased postoperative nausea but did not change postoperative vomiting [23]. These subtle differences may result from the different dosages used by the type of surgery patients in these studies. Pethidine, used as a postoperative analgesic, can cause nausea and vomiting.

Previous study [24] have shown that female gender, longer anesthesia time, general anesthesia, not smoking, use of postoperative opioids, and previous postoperative nausea and vomiting(PONV) and/or motion sickness were associated with increased incidence and severity of postoperative nausea and vomiting(PONV). Although less important, PONV may also be influenced by the type of surgery as well: strabismus correction and laparoscopic surgery especially have been described as risk factors for postoperative nausea and vomiting (PONV). Most of the previous studies that addressed the effect of gabapentin on reducing postoperative nausea and vomiting (PONV) incidence and severity have been performed on laparoscopic surgery procedures [25]. Our study confirmed the previous studies8 involving the use of gabapentin in patients undergoing laparoscopic cholecystectomy. Pandey *et al*. [8] in a randomized double-blind placebo-controlled study showed that preoperative administration of 600 mg gabapentin significantly reduced the incidence of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy (46/125 vs. 75/125; p = 0.04). For pain control, it also reduced postoperative fentanyl use. However, it did not have any significant effect on the severity of postoperative nausea and vomiting (PONV). In another study, performed by Mohammadi and Seyedi [26] it was shown that 300 mg gabapentin given preoperatively significantly reduced the severity of postoperative nausea and vomiting (PONV). The need for additional analgesic after laparoscopic surgery for assisted reproductive technologies. But it did not reduce the incidence of postoperative nausea and vomiting. Apparently, gabapentin has also been shown to reduce the incidence of nausea and vomiting after chemotherapy by a postulated mechanism of mitigation of tachykinin euro transmitter activity [17]. The etiology of postoperative nausea and vomiting(PONV) particularly in patients undergoing Laparoscopic cholecystectomy is not identical to that in patients receiving cytotoxic drugs, but we assume that it may be one probable mechanism in the prevention of postoperative nausea and vomiting (PONV) by gabapentin. As all the variables were similar between study groups, the difference in the incidence of postoperative nausea and vomiting(PONV) could only be attributed to gabapentin. In the case of laparoscopic cholecystectomy, the effect of intra-peritoneal CO2 insufflation on residual stretching and irritation of the peritoneum [27]. In a clinical study involving 17638 patients, the predictors for post-operative nausea and vomiting (PONV) were derived. This study demonstrated that an increase of 10 years in age decreased the likelihood of postoperative nausea and vomiting (PONV) by 13%; the risk for men was one-third that for women; a thirty minutes increase in the duration of anaesthesia increased the likelihood of Post-operative nausea and vomiting (PONV) by 59%, and general anesthesia increased the likelihood of Post-operative nausea and vomiting (PONV) by 11 times compared to other types of anesthesia [28]. A study in Finland and Germany enrolling 2722 patients identified four predictors for post-operative nausea and vomiting (PONV) based on logistic regression coefficients: female gender, history of motion sickness, or postoperative nausea and vomiting (PONV), non-smoking, and use of postoperative opioids [29]. The incidence of postoperative nausea and vomiting (PONV) with each of the factors enumerated above was 10-21%, 39%, 61%, and 79%, respectively [7]. In our study both the groups were comparable with regard to the risk of suffering Post-operative nausea and vomiting(PONV) (gender distribution; exclusion of patients with the history of motion sickness or postoperative nausea and vomiting(PONV) or history of smoking; and use of postoperative opioids for pain management). This study showed that there are statistically significant differences between the study and control groups regarding mild (p=0.039) and moderate grade (p=0.043) of postoperative nausea and vomiting (PONV). In severe grade (p=0.075), no statistically significant difference was found. Our results were in contrast to the findings of Pandey *et al*. [30].

LIMITATIONS OF THE STUDY

This was a double-blinded, single-centered study. The duration was short. Does not proclaim the scenario of the whole country.

CONCLUSION

This study revealed a significantly higher efficacy of prophylactic gabapentine in reducing post-operative nausea and vomiting. Regarding the question of the severity of postoperative nausea and vomiting (PONV), this study has shown a mixed pattern of results. It requires further study to clarify the mechanism influencing the severity of postoperative nausea and vomiting (PONV).

RECOMMENDATIONS

A multicentered double-blinded study in the divisional/ tertiary hospitals of whole Bangladesh can reveal the real picture regarding the efficacy of gabapentine in preventing postoperative nausea and vomiting(PONV) in case of laparoscopic cholecystectomy. The study period should belong. A multi-disciplinary approach to research work can make a study precise and more authentic in this regard.

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