THE EFFICACY OF APREPITANT (NK-1 RECEPTOR ANTAGONIST) AS PROPHYLAXIS FOR POSTOPERATIVE NAUSEA AND VOMITING

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ABSTRACT

Objective: To assess the effectiveness of Aprepitant (NK-1 receptor antagonist) for prophylaxis of postoperative nausea and vomiting in middle aged female patients undergoing laparoscopic cholecystectomy under General Anesthesia.

Study Design: Quasi-experimental study.

Place and Duration of Study: Combined Military Hospital Lahore, from Jun 2018 to Dec 2018.

Methodology: Four hundred American Society of Anesthesiologists (ASA) I and II middle aged female patients undergoing laparoscopic cholecystectomy under general anesthesia were recruited. Patients were divided into two groups of 200 each as "A" (Aprepitant) and "P" (Placebo). Forty miligrams Aprepitant was given to A-group patients, whereas P-group was given empty capsule. Patients were given standardized general anesthesia and were observed and documented for incidence and severity of early (0-2 hours) and delayed (2-24 hours) periods for episodes of postoperative nausea and vomiting.

Results: In A-group 20 (10%) had nausea, 8 (4%) had vomiting. Only 4 (2%) needed rescue anti-emetic. In P-group 84 (42%) had nausea and 76 (38%) had vomiting, 21 (10.5%) needed rescue antiemetic. The difference between the two groups was found statistically significant.

Conclusion: Preemptive use of Aprepitant (NK-1 receptor antagonist) reduces the incidence of postoperative nausea and vomiting and need for rescue anti-emetic.

Keywords: Aprepitant (Neurokinin-1 receptor antagonist), Postoperative Nausea and Vomiting, Prophylaxis.

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INTRODUCTION

Nausea is an unpleasant feel and urge to vomit and vomiting is forceful expulsion of gastric contents in a reflux mechanism against a closed glottis[1,2]. Postoperative nausea and vomiting (PONV) is one of the most distressing conditions for the patient and equally unpleasant for relatives[1]. Incidence of PONV ranges from 30-70% in different studies. It has got many adverse effects like increase in pain intensity, wound dehiscence, hemorrhage, hematoma formation, gastric aspiration, fluid and electrolyte imbalance, and delayed discharge or re-admission in the hospital[1].

Nausea and vomiting are affected by complex set of receptors and central nervous system nuclei[2]. Receptors involved in PONV are cholinergic, dopaminergic, histaminic, serotonergic and NK-1 receptors. There is no specified vomiting center but neurons involved are spread throughout the medulla oblongata. Chemoreceptor trigger zone (CTZ) area is strongly associated with vomiting process and it is located in the area postrema located in the floor of fourth ventricle. Vomiting centers receive afferent input from higher cortical areas, the cerebellum, vestibular apparatus, and vagal and glossopharyngeal nerves[2].

Many drugs belonging to different chemical groups have been tried alone or in combination with varied percentage of success because of diverse nature of receptors and brain centers and mechanisms[2,3].

Dopamine antagonists Metoclopramide and Droperidol are among the first anti-emetics class, with association of extrapyramidal effects,

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Received: 06 May 2019; revised received: 27 Aug 2019; accepted: 27 Aug 2019

insomnia, sedation and anxiety with the former and potentially life threatening dysrhythmias and clinically relevant prolongation of QTc interval at high doses with the later[4]. Anti-histamines e.g. Promethazine, act on histamine receptors in the vomiting center, but unfortunately result in sedation and dry mouth. Anti-cholinergic Scopolamine patches can stop vomiting, but its unwanted effects aredry mouth, sedation, blurred vision and confusion[2-4].

Serotonin antagonists (Ondansetron) although very efficientcan have side effects like headache, constipation and disturbed liver enzymes. Dexamethasone is effective in combination with other anti-emetic agents but its side effects include adrenal insufficiency, immunosuppression and water retention[4]. Common triple therapy regimen is followed for highly prone patients for PONV which includes Droperidol, Promethazine and Dexamethasone[5].

None of the so far available anti-emetics are 100% successful in the management of PONV, rather they are associated with many undesirable effects, so quest for an ideal drug still remains[6].

There are multiple factors which determine the incidence and severity of PONV like the patient, type of surgery and anesthesia. Patient factors include gender, smoking status, BMI, history of emesis and anxiety level. Types of surgeries which are more prone to PONV include laparoscopic, strabismus surgery in children, orthopedic, thyroid, breast, ENT, plastic and gynecological surgeries[6]. Anesthesia related factors are opioids, inhalational anesthetic agents, Nitrous Oxide, duration and anesthetic complications[6].

Newer class of drugs such as serotonin receptor antagonists and neurokinin-1 (NK-1) receptor antagonist have better safety profile and are more effective than previously used drugs[7]. Aprepitant is NK-1 receptor antagonist which is highly selective and centrally acting with half-life of 9 to 12 hours. Empirical formula of Aprepitant is C23H21F7N4O3, It produces antiemetic effects by blocking substance P through antagonization of NK-1 receptors[8]. Aprepitant is made of morpholine core with two substituents attached to adjacent ring carbons. It has three chiral centers very close together, which combine to produce an amino acetyl arrangement[8].

Gaddum and Schild discovered Substance P which belongs to tachykinin family of neuropeptides[9]. Recent research has recognized that substance P is a major neurotransmitter in afferent pathways of emesis in the CNS. Substance P may also be released from enterochromaffin cells in the stomach and intestine and from sensory peripheral nervous system[10].

Purpose of this study is to measure the effectiveness of Aprepitant (NK-1 receptor antagonist) in the prophylaxis of PONV in female patients undergoing laparoscopic cholecystectomy under GA.

METHODOLOGY

This study was carried out on 400 ASA I and II, middle aged (40–60 years) female patients undergoing laparoscopic cholecystectomy under general anesthesia by adopting non probability convenience sampling technique. Approval from the hospital ethical committee and informed written consent was obtained from all the patients undergoing the study. Hepatitis B or C positive, morbidly obese, and patients having known hypersensitivity to Aprepitant were excluded from the study.

Patients were divided randomly into two groups of 200 each as “A” (Aprepitant) and “P” (Placebo) group using random allocation table. A-group patients received oral Aprepitant capsule 40mg approximately 2 hours before general anesthesia with a sip of water and P-group were given empty capsule to act as placebo. Patients were counseled about PONV and were explained about an interview in postoperative period regarding subjective feeling of PONV. Intensity of nausea was described on VAS scale as 0 to 3 (0 for nil, 1 for mild, 2 for moderate and 3 for severe). Severity of vomiting was evaluated in terms of number of episodes.

Anesthesia regimen was standardized for all the patients in the study. Intravenous Midazolam 2mg and Dexamethasone 10mg were used for premedication. Anesthesia was induced with intravenous Propofol 1.5–2.5mg/kg and maintained with 1 MAC of Isoflurane. Intravenous Nalbuphine 10mg for analgesia and intravenous Atracurium 0.5mg/kg for muscle relaxation were given.

Rescue therapy for PONV was provided with 4mg of intravenous Ondansetron while postoperative pain was managed with a combination of intravenous Ketorolac and Nalbuphine.

Frequency and intensity of PONV was observed and documented by an anesthesia consultant or a post graduate resident during early (0 to 2 hours) and delayed (2 to 24 hours) periods. Mean, standard deviation and percentages were calculated using Microsoft excel. A *p*-value was calculated using independent samples t-test for confounding variables and chi square test for categorical variables.

RESULTS

Patients under study had the following demographic data and analyzed results:

Table-I and II depict that there was no statistically significant difference between the confounding variables.

Table-I: Demographic data.

Variables	A-Group (n=200)	P-Group (n=200)	*p*-value
Age, years (Mean ± SD)	44.7 ± 6.8	43.6 ± 6.9	0.1091
BMI, kg/m² (Mean ± SD)	30.398 ± 4.4	29.939 ± 5.3	0.3466
ASA status	I, II	I, II	-
History of Motion sickness	30 (15%)	29 (14.5%)	0.8880
Menstruation	4 (2%)	5 (2.5%)	0.7363
Smoking	2 (1%)	1 (0.5%)	0.5627

Table-II: Duration of surgery/anesthesia.

Variables	A-Group (n=200)	P-Group (n=200)	*p*-value
Duration of surgery, min (Mean ± SD)	81.57 ± 32.77	83.12 ± 12.32	0.5316
Duration of anesthesia, min (Mean ± SD)	91.46 ± 34.23	94.13 ± 17.21	0.3249
Intra-op intravenous fluids, ml (Mean ± SD)	648.66 ± 140.7	661.57 ± 22.65	0.2009
Surgical/Anesthetic complications	5 surgical complications (Percentage 2.5%)	3 surgical complications (Percentage 1.5%)	0.4756

Table-III: Incidence of PONV & need for rescue anti-emetic in both groups.

Group-A	Nausea		Vomiting		Rescue Anti Emetic	
	Early	Delayed	Early	Delayed	Early	Delayed
A-Group (n=200)	11 (5.5%)	9 (4.5%)	6 (3%)	2 (1%)	2 (1%)	2 (1%)
P-Group (n=200)	46 (23%)	39 (19.5%)	37 (18.5%)	46 (23%)	9 (4.5%)	12 (6%)

Group-B	Total Patient With Nausea & Vomiting			*p*-value		
	Nausea	Vomiting	Rescue Anti Emetic	Nausea	Vomiting	Rescue Anti Emetic
A-Group (n=200)	20 (10%)	8 (04%)	4 (02%)	<0.001	<0.001	<0.001
P-Group (n=200)	85 (42%)	76 (38%)	21 (10.5%)			

Table-II & III reveal that there was statistically significant difference between the two groups in terms of nausea, vomiting and rescue anti emetic (p<0.001).

DISCUSSION

Although mortality from anesthesia is a major disaster but luckily it is rare in developed health care services[11]. Hence the focus is on the quality of anesthesia and service improvements and prevention of PONV is major issue in this regard[12]. Despite major advancements, emesis

remains a significant nuisance in the post-operative period and during cancer chemotherapy[13].

Multiple ''willingness to pay'' research studies have revealed that the patient's greatest fear is PONV, even greater than the phobia of death itself[14]. Thus a pharmacological quest for a strongly effective anti-emetic has compelled the scientists to explore the role of various neuro-humoral factors[15].

The discovery of selective 5-HT3 receptor antagonist achieved a major success in this regard. These drugs were publicized to have resolved the problem of PONV; unluckily this was not the case. This challenging aspect gave the motivationfor the developing concept of combined therapies for PONV, which is regarded as more efficacious than mono-therapy[16].

Aprepitant has been recently introduced in Pakistan and mostly it has been used to control vomiting in cancer patients. PONV remains the major postoperative complication in developing countries partly due to lack of awareness in healthcare providers.

Our study had extremely encouraging results as only 10% of patients had complaints of nausea and even fewer (4%) had vomiting (p<0.001). Rescue therapy was needed only in 2% patients and none of the patients developed serious complication because of PONV. Patients in placebo group had incidence of vomiting up to 38% and nausea up to 42% which is significantly higher than those who received Aprepitant for prophylaxis (p<0.001). Hence the difference between the two groups was found to be statistically significant.

Currently there are many drugs in various stages of development in the world. Pharmaceutical companies are more interested in development of antiemetic drugs for chemotherapy patients than PONV and new anti-emetics are often first tested for that indication, this applies also to the NK-1 antagonists. The data on PONV are slightly more promising as some studies have shown NK-1 antagonists to be more effective than 5-HT antagonists[17]. Apfel *et al* in their recent review of current data expressed that the anti-vomiting properties of Aprepitant are distinctive and it is more effective against nausea than any other agents[18].

Potential efficacy of the NK-1 antagonists using pilot drugs as prophylaxis was described in two gynecological studies. Randomized control trials comparing the effects of Aprepitant vs Ondansetron in open and laparoscopic abdominal surgery also found it to be effective pharmacological mean for the prevention of PONV. Aprepitant was found to be superior to Ondansetron for of vomiting in the early period postoperatively, but similar to Ondansetron in prevention of nausea[19]. Similar studies from Korea and Japan had comparable results in prophylaxis PONV in gynecological laparoscopic surgery. All three trials demonstrated a statistically significant reduction in PONV both in immediate and delayed postoperative periods. They used higher dose of Aprepitant (80mg) than in our study[20].

Singhal *et al* carried out a meta-analysis comparing the effectiveness of 5HT3 antagonists against all non–5HT3 antagonists based on pharmacological approaches as a preemptive strategy for PONV in women undergoing breast surgery. These trials proved Ondansetron as superior drug for prophylaxis of PONV[21].

Lee and Fan performed a systematic review of acupuncturebefore surgery to prevent PONV and determined that acupuncture point stimulation, appear to prevent vomiting with negligible side effects[22].

It is beyond doubt that NK-1 antagonists have significant efficacy for PONV as our and many international studies suggest. Hence, Aprepitant seems to be an attractive drug for prophylaxis of high risk cases of PONV. Although not indicated for PONV, an intravenous form possibly used for the high risk patients of PONV. Other NK-1 receptor antagonists in the process of developmentare: Casopitant, Rolapitant and Vestipitant[23].

However, the data so far collected on PONV is comparatively deficient and further research is needed to illuminate the full image with confidence. Various studies indicate that these drugs have not yet become the long awaited ultimate solution to this menacing problem in certain respects; as NK-1 receptor antagonists will not replace the requirement for combined therapy in high risk cases and still preoperative risk evaluation for PONV is desired[24]. Protocol driven management of this fearsome and sometimes threatening postoperative complication is mandatory[25].

CONCLUSION

Preemptive use of Aprepitant (NK-1 receptor antagonist) reduces the incidence of postoperative nausea and vomiting and need for rescue anti-emetic.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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