INTRODUCTION

Nausea and vomiting are human protective reflexes against the absorption of toxins, as well as responses to certain stimuli. These symptoms are frequently listed by patients as their most important peri-operative concern. In the era of ether, the incidence of Postoperative Nausea and Vomiting (PONV) was as high as 75%. Despite advent of new technology and pharmacology, the incidence of PONV is still 20-30%. PONV can lead to serious complications such as aspiration, dehydration, electrolyte disturbances and disruption of incision site. It can also lead to increase cost of treatment, especially in outpatient surgical setting and unplanned hospital admission. Another impact of PONV, is the effect on patient, some regard it as more disabling than the operation itself.

ABSTRACT

Objective: To compare the efficacy of combination of dexamethasone plus ondansetron with dexamethasone alone for postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

Study Design: Double blinded randomized controlled clinical trial.

Place and Duration of Study: Department of Anaesthesiology, Surgical Intensive Care Unit and Pain Management, Dow University of Health Sciences and Civil Hospital, Karachi, from March 2007 to September 2007.

Patients and Methods: One hundred patients, both male and female, age 20 to 50 years, ASA Physical status I and II, scheduled for elective laparoscopic cholecystectomy under general anaesthesia were randomly allocated to two groups. Group A received dexamethasone (2 ml) plus ondansetron 4 mg (2 ml) prepared in two different syringes, and group B received dexamethasone 8 mg (2 ml) and normal saline (2 ml), prepared in two separate syringes just before induction of anaesthesia. Anaesthesia was standardized. For the first 24 hours after anaesthesia, the presence or absence of nausea and vomiting (by simply yes or no) was assessed by anaesthetist blinded to randomization. The rescue antiemetic (metoclopramide 10 mg) i.v., was given, if patient remained nauseous for more than 15 minutes, or experience retching or vomiting during study period.

Results: In comparison to dexamethasone group, the frequency of nausea and vomiting was clinically and statistically lower in dexamethasone – ondansetron group (p=0.035). Use of rescue antiemetic was significantly higher in dexamethasone group (p=0.022). Two patients in group A and one patient in group B experienced peri-anal itching at time of giving dexamethasone, none of our patients experienced headache, flushing or other side effects.

Conclusion: Combination of dexamethasone plus ondansetron is more effective in preventing postoperative nausea and vomiting than dexamethasone alone when used for prophylaxis of PONV before the induction of anaesthesia in patients undergoing laparoscopic cholecystectomy.


INTRODUCTION

Nausea and vomiting are human protective reflexes against the absorption of toxins, as well as responses to certain stimuli. These symptoms are frequently listed by patients as their most important peri-operative concern. In the era of ether, the incidence of Postoperative Nausea and Vomiting (PONV) was as high as 75%. Despite advent of new technology and pharmacology, the incidence of PONV is still 20-30%. PONV can lead to serious complications such as aspiration, dehydration, electrolyte disturbances and disruption of incision site. It can also lead to increase cost of treatment, especially in outpatient surgical setting and unplanned hospital admission. Another impact of PONV, is the effect on patient, some regard it as more disabling than the operation itself.

The causes of PONV are multiple, including pharyngeal stimulation, gastrointestinal distention, abdominal distention, abdominal surgery, anaesthetic agent, pain, opioids, hypoxia, hypotension, vestibular disturbances and psychological factors. There are certain factors which can pre-dispose patient to postoperative nausea and vomiting, like age (more in children), gender (female), history of previous nausea and vomiting, history of motion sickness, long-duration of operation and depth of anaesthesia, carbon dioxide retention, rough handling, lack of anaesthetist’s skill, type of surgical procedure and number of visitors during recovery.

Laparoscopic Cholecystectomy (LC) is being practiced for many years. The advantage of shorter hospital stay and more rapid recovery to normal activities with less pain associated with small incision and less post-operative ileus makes it more popular day by day. However, according to literature, incidence of PONV in laparoscopic cholecystectomy is approximately 70%. Although exact etiology of such a high incidence of PONV in laparoscopic surgery is not fully known, associated risk factors include: carbon dioxide insufflations, peritoneum distension, diaphragmatic irritation and visceral organ irritation and manipulation.
PONV is multifactorial during laparoscopic cholecystectomy, and none of the available antiemetic can antagonize all neurotransmitter system. A combination of different classes of antiemetics are, therefore, preferred to control PONV in high risk surgical patients. 

Dexamethasone has been used as an antiemetic for more than 20 years in patients undergoing chemotherapy with limited side effects. Recent studies have shown its efficacy as a prophylactic agent for PONV in high risk patients. Ondansetron, a 5-HT3 (5 Hydroxy-tryptamine Type 3) receptor antagonist, has provided effective antiemesis in surgical patients. The combination of these two agents could provide a more effective alternative. This combination has not been studied in our country for prevention of PONV. Therefore, present study was designed to assess the efficacy of ondansetron-dexamethasone combination for prevention of PONV in patients undergoing laparoscopic cholecystectomy.

PATIENTS AND METHODS

It was a double blind randomized controlled clinical trial carried out from March 2007 to September 2007 at Department of Anaesthesiology, Surgical Intensive Care Unit and Pain Management, Dow University of Health Sciences and Civil Hospital, Karachi, after approval from hospital ethics committee.

One hundred patients, both male and female, age 20 to 50 years, ASA physical status I and II, scheduled for elective laparoscopic cholecystectomy under general anaesthesia were included in this study. Patients who refused to be included in this study, ASA physical status III and IV, ASA I or II with history of hypertension or diabetes, patient with history of allergic reaction to any drug or food, body mass index > 25 kg/m², history of motion sickness, history of previous nausea and vomiting, history of alcohol or drug abuse, history of taking any antiemetic agent with 24 hours, history of motion sickness, history of previous nausea and vomiting, history of alcohol or drug abuse, history of taking any antiemetic agent with 24 hours, history of smoking, conversion to open cholecystectomy, associated pregnancy and chronic cough were excluded from the study.

Patients scheduled for general anaesthesia were assessed day before the surgery. Informed written consent was obtained and then selected patients were randomly allocated into two groups (50 patients in each) by ballotting i.e. group A to receive dexamethasone (2 ml) plus ondansetron 4 mg (2 ml) prepared in two different syringes, and group B to receive dexamethasone 8 mg (2 ml) and normal saline (2 ml) prepared in two separate syringes. No premedications were prescribed.

On arrival in Operation Theatre, routine monitoring was applied and baseline haemodynamic parameters were recorded. Eighteen gauge cannula was inserted into a vein on the dorsum of hand. All patients received 100% oxygen before the induction of anaesthesia for 5 minutes. The study agents were injected according to group of patient, one minute before the induction of anaesthesia; any side effect during injection was also recorded. Anaesthesia was induced with propofol 2.5 mg/kg and nalbuphine 0.2 mg/kg. Trachea was intubated with appropriate size endotracheal tube 3 minutes after tracurium (0.5 mg/kg). Ventilation was controlled mechanically and adjusted to keep end-tidal carbon dioxide between 40-50 mm of Hg. A nasogastric tube was passed to promote baseline emptying of the stomach of air and gastric contents. Anaesthesia was maintained with isoflurane, 40% oxygen in nitrous oxide. During surgery, patients was placed in reversed Trendelenburg position with right side of table elevated. The abdomen was insufflated with carbon dioxide, with intra-abdominal pressure of 10-16 mm of Hg. Anaesthesia was performed by the same team.

At the end of surgery, volatile agent and nitrous oxide were turned off, ketorolac 30 mg was given for postoperative pain control and wound was infiltrated with 0.5% bupivacaine. Neostigmine 2.5 mg with glycopyrrolate 0.5 mg was given for reversal of neuromuscular block and trachea was extubated on regaining spontaneous breathing and opening of the eyes. Nasogastric tube was also removed at the end of surgery before extubation.

For the first 24 hours after anaesthesia, the presence or absence of nausea and vomiting (by simply yes or no) was assessed by anaesthetist, who had no knowledge of drug given to patient, similarly, patients were also blind to drug given to them. Any side effects in postoperative period were also recorded.

The rescue antiemetic (metoclopramide 10 mg), i.e. was given, if patient remained nauseous for more than 15 minutes, or experienced retching or vomiting.

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences). Quantitative variables were expressed as mean ± SD (standard deviation), while qualitative variables were expressed as percentage. Age, weight, duration of surgery and duration of anaesthesia were analyzed by using student t-test, while gender, ASA physical status, frequency of nausea and vomiting and use of rescue antiemetic were analyzed by using chi-square test. P-value less than 0.05 was considered significant.

RESULTS

One hundred patients, 50 in each group were initially selected for this study. However, one patient in group A and 2 patients in group B were not included in statistical analysis because of conversion to open cholecystectomy leaving the study sample to 97 patients.

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Both groups were comparable with regards to age (p=0.240), gender (p=0.553), ASA physical status (0.530) and weight (p=0.548), duration of surgeries (p=0.544), and duration of anaesthesia (p=0.872) as shown in Table I.

Table I: Demographic data.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group-A</th>
<th>Group-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.4 ± 8.2</td>
<td>39.3 ± 8.6</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>5/44</td>
<td>7/41</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>33/16</td>
<td>29/19</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68.9 ± 5.6</td>
<td>69.02 ± 6.3</td>
</tr>
<tr>
<td>Duration of surgeries (minutes)</td>
<td>61.9 ± 8.1</td>
<td>62.9 ± 7.8</td>
</tr>
<tr>
<td>Duration of anaesthesia (minutes)</td>
<td>88.0 ± 5.9</td>
<td>88.2 ± 5.5</td>
</tr>
</tbody>
</table>

In comparison to dexamethasone group, the frequency of nausea and vomiting was clinically and statistically lower in dexamethasone+ondansetron group (p=0.035, Figure 1). Out of 49 patients in group A, 81.6% did not have nausea or vomiting postoperatively, while 18.4% experienced nausea in this group. In group B, 33.3% had nausea, 6.3% had vomiting, while 60.4% did not complain of either nausea or vomiting.

Use of rescue antiemetic shown in Figure 2, was significantly higher in dexamethasone group (p=0.022).

Two patients in group A and one patient in group B experienced peri-anal itching at the time of giving dexamethasone, none of the patients experienced headache, flushing or other side effects.

DISCUSSION

This study shows that compared with dexamethasone 8 mg alone, dexamethasone 8 mg plus ondansetron 4mg intravenously, administered in combination to patients undergoing laparoscopic cholecystectomy, significantly decreases the frequency of PONV. Ondansetron is 5-HT3 receptor antagonist, which is effective in preventing PONV. The effectiveness of intravenous (i.v.) ondansetron as prophylactic postoperative antiemetic was evaluated by McKenzie and colleagues in dose ranging study. A smaller dose of ondansetron was chosen in this study for combination with dexamethasone 8 mg because previous data indicated that ondansetron either 4 mg or 8 mg were equally effective in prophylaxis of PONV. Secondly, both doses are reported to be equally safer after rapid intravenous administration in terms of cardiovascular adverse effects.

Dexamethasone was first reported as an antiemetic in patients receiving cancer chemotherapy in 1981. Recently, dexamethasone has been reported to be effective in preventing PONV in patients receiving tonsillectomy, thyroidectomy, abdominal hysterectomy and laparoscopic cholecystectomy. A wide range of doses of dexamethasone (8-32 mg) has been used in the management of PONV and emesis associated with chemotherapy. Among these doses 8-10 mg has been used most frequently in the prevention of PONV, hence, 8 mg dose was chosen for the present study.

The exact mechanism of antiemetic action of dexamethasone is not known. However, there has been some suggestions, such as central or peripheral inhibition of production or secretion of serotonin, central inhibition of the synthesis of prostaglandins or changes in permeability of the blood-brain barrier to serum proteins.

In this study, it was not possible to determine whether dexamethasone monotherapy had an antiemetic effect because no placebo group was included. However, a complete response (no nausea/vomiting) was observed in 60.4% of patients in dexamethasone group in this study. Previous studies reported a varying incidence of PONV after using dexamethasone as a prophylaxis. López-Olaondo and colleagues used 8mg of dexamethasone in patients undergoing gynaecological
surgery. They observed complete response after 48 hours of surgery in 60% of patients in dexamethasone group, an observation, which support our findings. The results are also supported by study conducted by Laïq et al. in which 42% of patients complained of PONV. Similarly, Biswas and colleagues observed complete response in 63% of patients undergoing laparoscopic tubal ligation. However, Wang and colleagues used dexamethasone and reported incidence of PONV as 23% in dexamethasone group. Ionescu and colleagues reported PONV in 20% of patients who received dexamethasone as prophylaxis undergoing cholecystectomy.10

Kashmiri et al. used dexamethasone 8 mg in patients undergoing laparoscopic cholecystectomy just before induction of anaesthesia. In their study, 27% of patient experienced PONV during first 12 hours and 30% patients reported nausea and vomiting in next 12 hours. The difference in these results could be due to use of different anaesthetic technique, different surgical approach, different type of surgery, use of opioids and postoperative analgesics, difference in patients population (male/ female), duration of anaesthesia and surgery.

A combination of dexamethasone and ondansetron being more effective in PONV prophylaxis, complements previous studies. López-Olaondo et al. concluded that prophylactic administration of a combination of dexamethasone and ondansetron is effective in preventing PONV in patients undergoing gynaecological surgery with fewer patients requiring rescue anti-emetics compared to other regimens of placebo, ondansetron or dexamethasone. Biswas et al. also found that combination of dexamethasone and ondansetron provided adequate control of PONV in patients undergoing laparoscopic tubal legation with overall complete response in 78% of patients. Similarly, Rajeeva et al. also found that a combination of dexamethasone and ondansetron is more effective as prophylaxis for postoperative nausea and vomiting with overall incidence of 8%. They suggested that delayed PONV (2-24 hours) was better controlled. However, in this study, the overall frequency of PONV was determined in 24 hours rather than at different intervals because of limited staff facilities. Henzi and colleagues in their meta-analysis concluded that currently best available prophylaxis for PONV is a combination of dextamethasone and 5-HT3 receptor antagonist.

A number of factors were kept constant in this study, like all patients received laparoscopic cholecystectomy. Anaesthesia was induced by the same team of anaesthetists. Anaesthetic technique was standardized, including postoperative analgesics. Duration of anaesthesia and surgery was comparable and there was no difference in age, gender and weight of patients in both groups.

Long-term corticosteroid therapy may have significant morbidity. However, side effects from brief (24-48 hours), or even high dose, corticosteroid treatment have been rare. In this study, peri-anal pruritus was observed in 3 patients. Neff and colleagues also reported excruciating peri-anal pain immediately after dexamethasone administration. The mechanism responsible for this phenomenon is not well-understood but is thought to be related to the phosphate ester of corticosteroid. Slow i.v. infusion of diluted dexamethasone can prevent this side effect.

CONCLUSION

Combination of dexamethasone plus ondansetron was more effective in preventing postoperative nausea and vomiting than dexamethasone alone when used for prophylaxis of PONV before the induction of anaesthesia in patients undergoing laparoscopic cholecystectomy.

REFERENCES

Comparison of dexamethasone plus ondansetron with dexamethasone alone for prevention of PONV in laparoscopic cholecystectomy


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