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# EFFICACY OF LEVOSULPIRIDE IN MINIMIZING POST-OPERATIVE NAUSEA & VOMITING AFTER LAPROSCOPIC CHOLECYSTECTOMY

**Renuka Sharma** Associate professor, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan

**Pradeep Goyal** Associate professor, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan

**Manish Wadhwa** Senior Resident, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan

**Money Gupta** Professor, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan

**Vishal Mandial** Assistant Professor, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan

**K S Jaswal** Professor, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan

## ABSTRACT

**Background:** Gallstone disease and its symptoms are frequently encountered in Indian population. Approximately, 80% of the gallstones are asymptomatic. Female sex, obesity, pregnancy, rapid weight loss, gallbladder stasis, and increasing age are a few risk factors for the development of gallstones.

**Materials and Methods:** The present study was conducted over a period of one year in the Department of Surgery from January 2018 to December, 2018. Patients admitted in the Department of Surgery for elective laparoscopic cholecystecytomy were enrolled in the study after fulfilling the eligibility criteria. The patients were allocated into 2 groups of 50 patients each on the basis of random sampling method.

**Result:** Pre-operative administration of injection levosulpiride 25 mg in patients undergoing elective laparoscopic cholecystectomy surgeries under general anesthesia significantly ($P<0.001$) reduces the incidence of pre-operative nausea & vomiting.

**Conclusion:** It was hence seen to improve the quality of patient care in early stage of post-operative rehabilitation and also decreases the duration of hospital stay.

## KEYWORD

Levosulpiride, Laproscopic Cholecystectomy

## ARTICLE HISTORY

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*Corresponding Author Dr. Pradeep Goyal

Associate professor, Department of General Surgery, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan, pattypatiala@rediffmail.com

## INTRODUCTION

Gallstone disease and its symptoms are frequently encountered in Indian population. Approximately, 80% of the gallstones are asymptomatic[1]. Female sex, obesity, pregnancy, rapid weight loss, gallbladder stasis, and increasing age are a few risk factors for the development of gallstones[1]. They usually present with symptoms like pain, dyspepsia or also can rarely lead to complications such as acute cholecystitis, common bile duct stones, and acute pancreatitis. The diagnosis is primarily based on the patients' anamnesis of pain attacks and the presence of gall stones. Since 1980, the presence of gallstones has been diagnosed by ultrasonography[2-15]. The main treatment of gallstones is surgery. Gallstone disease is associated with various psychological and social life sufferings in patients during their wait for surgery. Delayed surgery puts patients at risk for developing acute complications, requiring hospital admission and urgent treatment. There has been a reduction in morbidity, pain and fatigue postoperatively with laparoscopic surgery. Moreover, there is an obvious clinical advantage over the open surgery due to less metabolic stress response[16-28]. The procedure is performed in steep head-up tilt, usually under general anaesthesia with laproscopic access to the gall bladder after creating a pneumoper itoneum. Around 40-70% patients undergoing laproscopic cholecystectomy experience adverse effects in the form of pain, dyspepsia, postoperative nausea & vomiting (PONV) due to irritation of diaphragm & internal viscera due to $CO_2$ insufflation[16-19]. This can at times lead to severe electrolyte imbalance and hence delay in recovery of the patient. Several Medical measures have been described[20-28] to minimize PONV in these patients but their efficacy is still debatable. Recently, Levosulpride ( ) has been claimed to provide a significant relief to this group patient after Laparoscopic

Cholecystectomy. Therefore, we tried to evaluate its efficacy in minimizing PONV in our patients.

## MATERIALS AND METHODS

The present study was conducted over a period of one year (January 2018-December, 2018), in the Department of General Surgery, M.M. College and Hospital, K.H. Solan. Approval for study was obtained from Ethical Committee of the institute. Patients admitted in the department of general surgery for elective laparoscopic cholecystectomy were enrolled in the study after fulfilling the eligibility criteria. The patients were allocated to 2 groups of 50 patients each on the basis of random sampling method.

### Inclusion Criteria

1. Patients posted for elective laparoscopic cholecystec tomy surgeries.
2. Patients of either sex, between the age group 20 and 50 years.
3. Patients weighing between 40 to 70 kg.
4. Patient willing to participate in the study and giving a written informed consent.

### Exclusion Criteria

1. Patient refusal.
2. Patients with known hypersensitivity or contraindications to study drug.
3. Patients coming for any emergency surgeries.
4. Patient age >50 years and <20 years.
5. Patients with a history of motion sickness.

## METHODOLOGY

The patients were randomly allocated into 2 groups:
Group L: Received injection Levosulpiride 25 mg iv along with standard medication prior to surgery.

Group C: Only received standard medication prior to surgery.

Postoperatively, patients were advised to take rest and remain in the bed at least for the first 24 hours. Other emetogenic analgesics and drugs were avoided in the first 24 hours. The number of episodes of nausea and vomiting and side effects of levosulpiride, if any, were assessed postoperatively for 24 h. The above findings were recorded in the following intervals: 0-4 h, 4-8 h, 8-12 h & 12-24 h in the post-operative period and were statistically analysed accordingly. Rescue antiemetic consisting of injection metoclopromide 10 mg iv was given after vomiting.

## RESULTS

The present study was conducted over a period of one year between January 2018 to December, 2018 in the Department of General Surgery, M.M. College and Hospital, K.H. Solan, H.P. The patient population (n=100) was randomized into two groups as study (n=50) and control(n=50). Patients in the study group received injection Levosulpiride 25mg iv just before surgery along with the standard care, whereas the control group received only standard care.

### Demographic of Patient population:

**Age:** The age range of the study population ranged from 21 to 50 years with a mean age of 30.03±7.55 years, whereas, it was 23-50 years for the control group with a mean of 37.9±8.7 years.

**Gender:** The overall male to female ratio was 2:3 and was similar in both the groups.

**Weight:** The mean weight in the study group was 59.67±6.9 kg and for control group was 58.27±8.14kg.

General patient profile along with clinical signs & symptoms of study & control group

**Table: 1**

| | Study group (n=50) | Control group (n=50) |
|---|---|---|
| Age (in years) | (39.03+7.55) 21-50 years | (37.9±8.7) 23-50 years |
| Gender (M:F) | 12M & 18 F (2:3) | 13M & 17 (2:3) |
| Weight (in kg) | 59.67±6.91 | 58.27±8.14 |
| Duration of illness | 1-3 years | 1-3 years |
| **Clinical signs & symptoms** | | |
| a) Pain in Right Hypochondrium | 35 (70%) | 33 (66%) |
| b)Flatulant Dyspepsia | 8(16.7%) | 7 (14%) |
| c)Pain epigastrium | 1 (2%) | 1 (2%) |
| d)Incidental finding | 3 (10%) | 8(16%) |
| **Co-Morbid condition** | | |
| a) Diabetes | 7 (13.5%) | 5 (10%) |
| b) Hypertension | 1 (2%) | 3(6 %) |
| c) Both Diabetes & Hypertension | 1(2%) | - |

**Duration of illness:** The duration of illness ranged from 1 to 3 years in both, study as well as control group.

**Co-morbid conditions:** Both, study as well as control group had underlying Co-morbid conditions such diabetes and hypertension in 13.5%, 2% in study & 10%, 6 % in control group respectively. One patient had both diabetes as well as hypertension in the study group.

**Presenting clinical Signs & Symptoms:** The most common presenting clinical complaint was pain in the right hypochondrium in both study (n=35, 70%) and control group (n=33, 66%), followed by flatulent dyspepsia in 8 patients (16%) in study group & in 7 patients (14%) in control groups. Pain in the epigastrium was reported by only one patient in both the groups.

**Ultra-sonographic evaluation:** USG evaluation was done in both study as well as control group, in which 30 patients in control group had multiple calculi, 18 had a solitary stone. Thirty-five patients in study group had multiple calculi & 15 had solitary stone (Table-2)

**Table 2: Group comparison for USG findings**

| USG findings | Number of patients (%) | Number of patients (%) |
|---|---|---|
| | Group L | Group C |
| GB Sluge | 0 (0.00) | 1 (2%) |
| Multiple calculi | 35 (70%) | 30(60%) |
| Solitary calculus | 15 (30%) | 18 (36%) |
| P value | 0.091 | |
| Remarks | NS | |

NS: Non-significant, USG: Ultrasonography

**Post-operative nausea & vomiting (PONV,** Table-3**) :**

**0-4 hours:** None of the patients in levosulpiride group had any nausea or vomiting within first 4 hours of the post-operative period, whereas 28 patients (56%) in the control group experienced nausea & vomiting during this period and this finding was statistically significant (p<0.0001).

**4-8 hours:** Twenty-seven (54%) patients in the control group and one (2%) in levosulpiride group experienced nausea or vomiting during this post-operative period and this difference was again statistically significant (p<0.0001).

**8-12 hours:** Twenty eight (56%) patients in the control group & ten (20%) in the study group experienced nausea or

vomiting during this period and this was also statistically significant.

**12-24 hours:** Twenty-three (46%) patients in the control group & eight (16%) in the study group experienced nausea or vomiting during this period and this was also statistically significant($p<0.001$).

**Table 3: Group comparison for PONV**

| Time interval (h) | Number of patients (%) | Number of patients (%) | *P* value | Remarks |
|---|---|---|---|---|
| | Group L (n=50) | Group C (n=50) | | |
| 0-4 | 0 (0.00) | 28 (56%) | <0.0001 | S |
| 4-8 | 1 (2%) | 27 (54%) | <0.001 | S |
| 8-12 | 10 (20%) | 28 (56%) | 0.001 | S |
| 12-24 | 8 (16%) | 23 (46%) | 0.001 | S |

S: Significant, PONV: Post-operative nausea and vomiting

In control group, 27 patients were given rescue antiemetics whereas in Levosulpiride group, only 11 patients received antiemetics, this difference was found to be statistically significantly ($p<0.002$), as shown in Table-4.

**Table 4: Group comparison for rescue antiemetic**

| Groups | Rescue antiemetic |
|---|---|
| | Number of patients (%) |
| Group L (n=50) | 11(22%) |
| Group C (n=50) | 27 (54%) |
| *P* value | 0.002 |
| Remarks | S |

S: Significant

The mean length of hospital stay was 2.33±0.48 days in control group, whereas it was 2.20±0.41 days in Levosulpiride group and was comparable (Table-5) in both the groups.

**Table 5: Group comparison for hospital stay**

| Groups | Duration of hospital stay (days) |
|---|---|
| | Mean±SD |
| Group L | 2.20±0.41 |
| Group C | 2.33±0.48 |
| *P* value | 0.251 |
| Remarks | S |

S: Significant, SD: Standard deviation

## DISCUSSION

PONV following laparoscopic cholecystectomy is of multifactorial origin. The incidence of PONV, despite the advances in antiemetic therapy in the past decades, it still causes, a lot of discomfort in large number of patients in the post-operative period. Factors affecting PONV include patient-related factors such as age, sex, phase of the menstrual cycle; anaesthesia related factors, such as, use of volatile anaesthetic agents, nitrous oxide (N2O), opioids and surgery-related factors[5]. Female gender has been associated with higher incidence of PONV compared to male patients. On an average, female patients suffer three times more often than men. Our study was aimed at evaluating the antiemetic efficacy of levosulpiride in preventing PONV in patients undergoing laparoscopic cholecystectomy. Laparoscopic surgery was chosen because of high incidence of PONV associated with it. Naguib *et al*[33] reported a remarkably high (72%) incidence of PONV after laparoscopic surgeries in their placebo group, which is comparable to the findings of our study, wherein, we observed an incidence of 56% (within first 12 hours) in the control group. A wide variety of antiemetic drugs (e.g., anticholinergics, antihistaminic, dopamine receptor antagonists, glucocorticoids, neurokinin-1 antagonists, etc.) are available to prevent post-operative emetic symptoms. Although phenothiazines, butyrophenones (domperidone), and metoclopramide are also antiemetic, they are associated with extrapyramidal side effects[34].

In our study, the females outnumbered the males in both the control and levosulpiride group. The mean age in of control group was 37.93 ± 8.73 years (range 20-50 years) and that in levosulpiride group it was from 39.03 ± 7.55 years (range 21-50 years). The mean weight of the control group was 58.27 ± 8.14 kg, whereas that of the levosulpiride group was 59.67 ± 6.91kg. Most patients studied, presented with pain in the Right Hypochondrium (70%), followed by flatulent dyspepsia (16%). Preoperatively, ultrasound was done in all cases, showing multiple calculi predominantly 70% & 60%, followed by solitary stone in 30% & 36% in study and control group respectively. Injection levosulpiride was administered 5 min before the induction of anaesthesia. During first 24 h after surgery, all episodes of nausea and vomiting and complete response at various time intervals, i. e., 0-4, 4-12, 12-24 h, were analysed statistically. In the control group, the incidence of PONV was 56% within 0-4 h, 54% from 4 to 8 h, 56% from 8 to 12 h and 46% from 12 to 24 h, compared to the levosulpiride group, in which the incidence of PONV was nil, 2%, 20% and 16% within the corresponding time intervals. Several factors, including sex, obesity and surgical procedure affect the incidence of post-operative nausea and vomiting[47] .The incidence of PONV seen in our control group significantly higher than the levosulpiride group and was comparable to many other recent studies in the literature[22-23]. This reflected the efficacy of pre-operative use of Levosulpiride, which is consistent with the other studies done by Fuji et al[15-16]. Statistically significant improvement was also seen in terms of usage of the rescue anti-emetic as only 9 out of 50 patients Levosulpiride group received them whereas 27out of 50 patients in control group were given rescue antiemetic in the post-operative phase. Thus, only one third of the patients received antiemetics in the levosulpiride group as compared to the control group, again reemphasizing the need for. Furthermore, a lesser duration of hospital stay was seen in the levosulpiride group. There was no evidence of any adverse events or o toxicities in the study group due to levosulpiride as commonly associated with other antiemetics, such as extrapyramidal signs and symptoms, cardiotoxicity and psychological disturbances[36]. In another study of over 200 patients by Kranke et al[24], wherein they showed that administration of amisulpride preoperatively reduced the incidence of PONV in adult surgical patients and these observations are in agreement with our findings. The incidence of PONV in our control group ranged from 46-56 percent and 2-20% in the levosulpiride group. Singh et al (2014) in a series of 113 patients divided into three groups (Group 1 levosulpiride 40 patients, Group 2 domperidone 35 patients, and Group 3 metoclopramide 38 patients) found a highly significant improvement in overall dyspeptic symptoms in the levosulpiride group ($P < 0.004$) as compared to domperidone and metoclopramide groups. Similarly, in our study, significantly lower incidence of nausea and vomiting was seen in the levosulpiride group ($P < 0.001$). Apfel et al[23] (2008) in a large series of 5000 patients demonstrated the benefit of a range of antiemetic interventions, including ondansetron, dexamethasone, and droperidol and found a relative risk reduction of ~25% compared with the absence of that intervention, equating to an absolute reduction of 15-20% points on a typical baseline PONV rate in the range 65-75%. This magnitude of benefit has been seen with many antiemetics in separate, placebo-controlled trials, including ondansetron (Fortney *et al.*)[14] and palonosetron (Kovac *et al.*, 2008)[23]. A cochrane collaboration meta-analysis, by Carlisle et al , of 737 studies involving 103,237 patients found that eight antiemetic agents tested were effective with a relative risk reductions in the range 20-40%. The benefit with injection levosulpiride 25 mg was a risk reduction of about 30%. The efficacy shown by levosulpiride appeared not to be at the expense of any toxicity or any other

extrapyramidal side effects. Hence Levosulpiride has several attractive features for use in patients undergoing laparoscopic cholecystectomy and appears to be quite promising to manage PONV in these patients.

In addition, it has a low propensity for drug interactions[44]; hence it can be safely used in elderly patients and in patients with renal failure. Thus, the present study demonstrates a significant benefit of preoperative administration of injection levosulpiride 25 mg in the prevention of PONV and significantly reduced the requirement of rescue anti-emetic and duration of hospital stay in the study group and thus improves quality of life postoperatively.

## CONCLUSIONS

The pre-operative administration of injection levosulpiride 25 mg in patients undergoing elective laparoscopic cholecystectomy surgeries under general anesthesia significantly reduces the incidence of PONV. It was hence seen to improve the quality of life in early stage of postoperative rehabilitation and also decreases the duration of hospital stay.

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