

# Efficacy of Levosulpride in minimizing Post-operative Nausea and Vomiting after Laparoscopic Cholecystectomy

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## ABSTRACT

**Introduction:** Gallstone disease is a common problem in our country. Approximately, 80% of the gallstones are asymptomatic. The risk factors predisposing to gallstone formation has been female sex, obesity, pregnancy, rapid weight loss, gallbladder stasis, and increasing age. Current study aimed to evaluate the efficacy of levosulpride in minimizing PONV in our patients.

**Material and Methods:** The present study was conducted over a period of one year in the Department of Surgery from January 2018 to December 2018. One hundred patients fulfilling the eligibility criteria for elective laparoscopic cholecystectomy were enrolled in the study and were randomly placed into 2 groups of fifty each.

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

**Conclusion:** levosulpride improved the quality of patient care in immediate post-operative phase and decreased the duration of hospital stay.

**Keywords:** Efficacy of Levosulpride, Post-operative Nausea, Vomiting after Laparoscopic Cholecystectomy

## INTRODUCTION

Gallstone disease is a common problem in our country. Approximately, 80% of the gallstones are asymptomatic. The risk factors predisposing to gallstone formation has been female sex, obesity, pregnancy, rapid weight loss, gallbladder stasis, and increasing age.<sup>1</sup> The patients commonly present with pain, dyspepsia, acute cholecystitis, rarely common bile duct stones and acute pancreatitis. The diagnosis of gallstones has been done traditionally by ultrasonography<sup>2-9</sup> and surgery has been the mainstay treatment for decades. Gallstone disease is associated with various psychological and social life sufferings in patients during their wait for surgery. Patients are at risk for developing acute complications in the event of delay in surgery which may require urgent hospital admission and treatment. Laparoscopic surgery has an obvious clinical advantage over open surgery in reducing postoperative pain, discomfort and other metabolic complications.<sup>10-16</sup> Laparoscopic access to the gall bladder is done in steep head-up tilt under general anesthesia after creating a pneumoperitoneum. Around 40-70% patients undergoing laparoscopic cholecystectomy experience adverse effects in the form of pain, dyspepsia, postoperative nausea and vomiting (PONV) due to irritation of diaphragm

and internal viscera due to CO<sub>2</sub> insufflation.<sup>16-19</sup> This can at times lead to severe electrolyte imbalance and hence delay in recovery of the patient. Several Medical measures have been described<sup>20-23</sup> 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.

## MATERIAL AND METHODS

The present study was carried out in the department of General Surgery, M.M. College and Hospital, K.H. Solan, Himachal Pradesh, from January to December, 2018. The study was approved by Ethical Committee of the institute. Patients admitted in the department of general surgery fulfilling the eligibility criteria for elective laparoscopic cholecystectomy were enrolled in the study after a written and informed consent and were randomly assigned into two groups of 50 each.

### Inclusion Criteria

1. Patient willing to participate in the study and giving a written informed consent
2. Patients listed for elective laparoscopic cholecystectomy.
3. Patients in the age group 20 and 50 years.
4. Patients having between 40 to 70 kg

### Exclusion Criteria

1. Patient refuse the surgery
2. Patients with known adverse effect to the study drug.
3. Emergency surgical intervention.
4. Patient less than 20 and more than 50 years of age.
5. Patients with a previous history of motion sickness.

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## Methodology

The patients were randomly assigned into 2 groups:

- Group L: Intravenous Injection of 25 mg Levosulpride along with standard medication prior to surgery.
- Group C: Only received standard medication prior to surgery.

A strict bed rest was advised to all the patients in the first 24 hours post-operatively. Other emetogenic and analgesic drugs were avoided in this period. The episodes of nausea, vomiting and adverse effects of levosulpride, if any, were assessed postoperative phase. These were recorded at: 0-4 h, 4-8 h, 8-12 h and 12-24 h in the post-operative phase and analyzed accordingly. Rescue antiemetic consisting of injection metoclopramide 10 mg iv was given after vomiting.

## RESULTS

The present study was carried out in the Department of General Surgery, M.M. College and Hospital, K.H. Solan, H.P, over a period of one year between January 2018 to December, 2018. The patient population (n=100) was randomized into

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

**Table-1:**

| USG findings                              | Number of patients (%) |          |
|---|------------------------|----------|
|   | Group L                | Group C  |
| GB Sludge                                 | 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 |                        |          |

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

| Time interval (h) | 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

**Table-3:** Group comparison for PONV

two groups as study (n=50) and control (n=50). Patients in the study group received injection Levosulpride 25 mg iv just before surgery along with the standard care, whereas the control group received only standard care.

### Demographic of Patient population (table-1)

**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 and symptoms of study and control group

**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 and 10%, 6% in control group respectively. One patient had both diabetes as well as hypertension in the study group.

**Presenting clinical Signs and 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 and 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 and 15 had solitary stone (Table-2)

### Post-operative nausea and vomiting (PONV, Table-3)

**0-4 hours:** None of the patients in levosulpride 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 and 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 levosulpride group experienced nausea or vomiting during this post-operative period and this difference was again statistically significant (p<0.0001).

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

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

| Groups                                 | Duration of hospital stay (days)<br>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 |   |

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

**8-12 hours:** Twenty eight (56%) patients in the control group and 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 and eight (16%) in the study group experienced nausea or vomiting during this period and this was also statistically significant ( $p < 0.001$ ).

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

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

## DISCUSSION

Post operative nausea and vomiting (PONV) after laparoscopic cholecystectomy is influenced by multiple factors. It causes a lot of discomfort to the patients in the post-operative phase despite recent advances in antiemetic therapy. PONV can be attributed either to patient-related factors such as age, sex, phase of the menstrual cycle or surgical and anaesthetic agent related, such as; volatile anaesthetic agents, nitrous oxide (N<sub>2</sub>O) and opioid use for pain relief.<sup>5</sup> Higher incidence of PONV has been observed in females as compared to male patients. In the present study we tried to evaluate the efficacy of levosulpride in preventing PONV in patients undergoing laparoscopic cholecystectomy. Naguib et al<sup>22</sup> 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. Different types of antiemetic agents, including various anticholinergics, antihistaminic, dopamine receptor antagonists, glucocorticoids, neurokinin-1 antagonists, have been tried to prevent post-operative nausea and vomiting. Certain other drugs tried as antiemetics like, phenothiazines, butyrophenone, and metoclopramide have been found to be

associated with extra pyramidal side effects.<sup>30</sup>

The female patients outnumbered the males in the control as well as study group. Mean patient age in the control group was  $38.73 \pm 8.37$  years (range 30- 65years) and  $36.03 \pm 6.75$  years (range 31-65 years) in the study group. Control group had a mean weight of  $57.72 \pm 6.14$  kg whereas it was  $58.76 \pm 7.19$  kg in the study group. Most patients studied, presented with pain in the right hypochondrium (70%), followed by flatulent dyspepsia (16%). Preoperative ultrasonography revealed multiple calculi both in study(70%) as well as control group(60%), and solitary stones in 30 and 36 percent in study and control groups respectively. Levosulpride was given intravenously 5 min prior to induction of anaesthesia. Subsequently the patients were monitored for nausea and vomiting at, 0-4, 4-12, 12-24 hours in the immediate post-operative phase. The incidence of these signs and symptoms were analyzed and compared in both the groups. 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, in the control group, whereas it was; nil, 2%, 20% and 16% for corresponding time intervals in the Levosulpride group. This was found to be statistically higher in the control as compared to the study group, clearly indicating the efficacy of levosulpride in minimizing the signs and symptoms post-operative nausea and vomiting. Several factors, including sex, obesity and surgical procedure affect the incidence of post-operative nausea and vomiting. The incidence of PONV seen in our control group significantly higher than the levosulpride group and was comparable to many other recent studies in the literature.<sup>22-23</sup> This has clearly shown that the use of Levosulpride in the pre-operative phase significantly reduces the incidence of PONV and is consistent with findings of Fuji et al<sup>16-17</sup> in their studies on this subject. The usage of the rescue anti-emetics was also significantly lower in the (9 out of 50 patients) Levosulpride group as compared to (27out of 50 patients) control group in the post-operative phase. Thus, only one third of the patients received rescue anti emetics in the levosulpride group as compared to the control group, again reemphasizing the need for. In addition the duration of hospital stay was longer in the control as compared to seen in the levosulpride group.

There was no evidence of any adverse events or toxicities in the study group due to levosulpride as commonly associated with other anti emetics, such as extra pyramidal signs and symptoms, cardio toxicity and psychological disturbances. In another study of over 200 patients by Kranke et al<sup>20</sup>, where in preoperative administration of amisulpride decreased the incidence of PONV in their 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 levosulpride group. In a study, including 113 patients, by Singh et al (2014) assigned into three groups of 40,35 and 38 patients receiving levosulpride, domperidone and metoclopramide respectively in the post-operative phase, observed statistically significant improvement in overall dyspeptic symptoms in the levosulpride 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 levosulpride group ( $P < 0.001$ ). In a large study of 5000 patients by Apfel et al<sup>21</sup> (2008) showed a relative risk reduction of ~25% in the PONV in patients receiving antiemetics, including ondansetron, dexamethasone, and droperidol and compared to the one's without any antiemetic therapy. Similar results has also been observed with many other antiemetics in case control trials by Fortney et al<sup>20</sup> and Kovac et al<sup>15</sup> in 2008. A cochrane collaboration meta-analysis, by Carlisle et al<sup>6</sup>, of 737 studies involving 103,237 patients found that eight antiemetic agents tested were effective with a relative risk reduction in the range 20-40%. The benefit with injection levosulpride 25 mg was a risk reduction of about 30%. Thus, the clinical benefit of levosulpride has clearly demonstrated without any adverse effects related to its toxicity or extrapyramidal manifestations.<sup>30</sup> Hence Levosulpride 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<sup>24-30</sup> hence it can be safely used in elderly as well as in patients with renal failure. Thus, the present study clearly demonstrates the efficacy of preoperative administration of injection levosulpride (25 mg) in the prevention of PONV and significantly reducing the requirement of rescue anti-emetics, duration of hospital stay resulting in overall improvement in patient care in the post-operative phase .

## CONCLUSION

Pre-operative levosulpride (25 mg) injection significantly reduces the incidence of PONV in elective laparoscopic cholecystectomy surgery. Thus, it helps in improving the quality of post-operative care, early recovery and reduction in the duration of hospital stay.

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