**Is infusion of sub hypnotic propofol as effective as dexamethasone in prevention of postoperative nausea and vomiting related to laparoscopic cholecystectomy?: A randomized controlled trial.**

**Short Title:** Effect of propofol in prevention of postoperative nausea and vomiting related to laparoscopic cholecystectomy.

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**ABSTRACT**

**Background:** Postoperative nausea and vomiting (PONV) are one of common complication undergoing patients laparoscopic cholecystectomy. Aim of this study was to compare the efficacy of sub hypnotic (1 mg/kg/h) infusion of propofol with dexamethasoneon postoperative vomiting in undergoing patients laparoscopic cholecystectomy(LC).

**Methods:** A total of 120 ASA physical status I and II were included in this randomized, double-blind, placebo-controlled study. Patients were randomly assigned to 3 groups (n=40) before induction of anesthesia. Patients of group dexamethasone (group D) were administrated 8 mg dexamethasone before induction of anesthesia. Patients of group propofol (group P) were infused to sub hypnotic (1 mg/kg/h) propofol during operation. Patients of group control (group C) were applied infusion of 10% intralipid until the end of surgery. The incidence of PONV, needs for rescue analgesic and antiemetic were recorded in the first 24 h postoperatively.

**Results:** In the 0-24 h, the incidence of PONV was significantly lower in the group D and group P compared with the group C (37.5%, 40%, 72.5% respectively). There was no significant difference in the incidence of PONV and use of antiemetics, analgesic between the group D and group P.

**Conclusion:** We concluded that infusion of propofol infusion 1 mg/kg/h is as effective as dexamethasone for the prevention of PONV during the first 24 hours after anesthesia in patients undergoing LC.

**Keywords:** Propofol, Dexamethasone, Postoperative Vomiting and Nausea

**Introduction**

Postoperative nausea and vomiting (PONV) are distressful common side-effects following laparoscopic cholecystectomy (LC) [1,2].The reported incidence of PONV is 46–72% in patients undergoing LC if prophylactic antiemetic is not given [3,4]

As an anesthetic agent, propofol is highly effective drug preventing postoperative nausea and vomiting [5), thus it has been used by a number of anesthesiologist [6].It was demonstrated that continuous infusion of sub hypnotic propofol prevents PONV in female patients receiving intravenous patient-controlled analgesia [7].

Glucocorticoids have analgesic, anti-inflammatory, immune-modulating and antiemetic effects. But, their effect mechanisms are not fully clarified [8]. Dexamethasone, as an glucocorticoid, has been used as an antiemetic drug in patients receiving chemotherapy for more than 25 years [9,10].Several prospective studies have shown that severity of PONV associated with LC is reduced by dexamethasone [11,12,13].

The primary aim of this prospective, randomized, double blind, placebo-controlled study was to evaluate the efficacy of dexamethasone and continuous infusion of sub hypnotic propofol to prevent PONV in patients undergoing LC. Secondary aim of this study was to determine the rescue antiemetic and analgesic in the first 24 hours after LC.

**Material and Methods:**

In this study, a total of 120 ASA I,II patients undergoing LC were included. The Institutional Review Board approved the study, and all 120 patients gave signed informed consent. Exclusion criteria were pregnancy, use of antiemetic drug 24 hours before LC, a history of vomiting and nausea in the previous operations, susceptibility to nausea and vomiting, menstruation, emergency operation, severe diabetes mellitus and conversion from LC to an laparotomy procedure.

Noninvasive blood pressure, ECG, pulse oximetry, and capnometry were used for patient’s monitoring during anesthesia. The patients were randomized using an equal number of blind envelopes and allocated to one of the three groups: Dexamethasone Group (Group D), Propofol Group (Group P) and Control Group (Group C). Before one minute of anesthesia induction, while patients in group D received 8 mg of dexamethasone, group P and group C received isotonic saline solution in 2 ml syringe. The same anesthetic techniques were used for all patients. Anesthesia was induced by 5 mg/kg of thiopental sodium, 1 mcg/kg fentanyl through intravenous cannula. Intubation of the trachea was facilitated with 0.6 mg/kg of rocuronium and subsequent intraoperative neuromuscular blockade was maintained with it. Anesthesia was maintained with 1.0–2.5% sevoflurane in 50 % oxygen and 1 mcg/kg/h fentanyl half an hour. All patients were inserted a nasogastric tube after anesthesia induction to empty content and air of stomach.. In group P, patients were given continuous propofol infusion at 1 mg/kg/h in during operation. In other two groups, suspension of 10% intralipid was infused in all patients. At end of surgery, neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and 0.01 mg/kg atropine sulphate. For postoperative analgesia, after operation, 10 ml local anesthetic solution (equally mixed 2% lidocaine plus 0.05% bupivacaine) was applied to incision region and preemptive analgesia was performed via intravenous 1 g of paracetamol and 1.5 mg/kg of tramadol.

Awakening time was defined as patient’s awakening (i.e., opening eyes at verbal command) and being orientated to the environment after discontinuation of the volatile agent.

All patients were observed for 24 hours by another anesthetist after surgery. These patients were informed about the scale of VAS (Visual analog scale) and PONV by the anesthetist. The incidence of nausea, vomiting and antiemetic requirement were recorded during three assessment periods, 0–6 h, 6–12 h, and 12–24 h after recovery from anesthesia using a four-point ordinal scale for PONV (0=none, 1=nausea, 2=nausea with request for antiemetic, 3=vomiting). Rescue antiemetic (intravenously metoclopramide 10 mg) was allowed by the anesthetist according to needs of patients. Intramuscular diclofenac sodium (50 mg) as analgesic was medicated when patients experienced pain of VAS > 3.

Statistical analysis was performed using the program of SPSS20. One way ANOVA was used to compare the differences of numeric data among the groups. Chi-squared test was used for categorical data. Level of significance was set at p < 0.05.

Before study, sample size was determined by power analysis, assuming that the total incidence of PONV in the placebo group would be 70%, with a 35% reduction in the incidence of PONV in the treatment group with alpha error was set at 0.05 and beta error at 0.2. According to power analysis, any group size of 31 patients was considered adequate. We decided to enroll 40 patients per group to allow dropout. The post-hoc test which was held during the statistical evaluation showed 31 patients for the propofol group and 35 patients for the dexamethasone group were needed.

**RESULTS**

All 120 patients had completed their surgical procedures. There was no statistically significant difference among the 3 groups in terms of age, body weight and height, ASA classification, duration of anesthesia, surgery and total fentanyl consumption (Table 1).

***Primary Outcome***

**Nausea and Vomiting**

During 0-6 h, total incidence of PONV was 65% in the group C, 30% in the group P and 30% in the group D. For 6-12 h ,it was 52.5% in the group C, 25% in the group P, 20% in group D. In 12-24 h period, it was 45% in the group C, 20% in the group P and 10% in the group D. In group D PONV was significantly lower than in group C at 0-6 h(**p =0.007)**, 6-12 h (***p=0.06)***, 12-24 h (***p=0.02***). Also patients group P had significantly less PONV than those of group C in the 0-6 h***(p=0.07)***, 6-12 h***(p=0.013)***, 12-24 h (***p= 0.039***).There were no significant differences between the Group D and Group P with regard to PONV.(Table 2)

***Secondary Outcome***

**Rescue antiemetic**

Four patients in group D, 4 patients in group P and 13 patients in group C were given antiemetic drug for 0-6 h. Patients in group D and group P had significantly less rescue antiemetic requirements than those of group C in this period (p=0.01 for both).One patient in the group D,3 patients in the group P and 8 patients in the group C were in need of rescue antiemetic drug during 6-12 h. Patients in group D had significantly lower antiemetic drug requirement than those of group P (p=0.01). There were no significant differences among the groups in 12-24 h in terms of antiemetic drug requirement. (Table 2)

**Analgesic Requirements**

In 0-24 h, 2 patients in the group D, 3 patients in the group P and 8 patients in the group C were treated with diclofenac sodium 50 mg via intramuscularly and difference between group D and group C was significant (p=0.04). (Table 3)

**Discussion**

Laparoscopic surgery has associated with high incidence of PONV(3,4). .Postoperative nausea and vomiting is an disagreeable, distressful, and fatiguing complication for patients undergoing LC vomiting. It might extend recovery time, delay of discharge time, higher hospital hosts [13] In our study, PONV in dexamethasone group and propofol group was significantly reduced compared with control group. However we found that infusion of propofol during the operation was as effective as dexamethasone to prevent of PONV.

The analgesic effects of the glucocorticoids are mainly related to the inhibition of the phospholipase enzyme pathway. Additionally they also decrease in pro inflammatory mediators such as interleukin-6 [14].

Dexamethasone use as an antiemetic agent in patients receiving cancer chemotherapy dates back to 1981. [9]. Although the mechanism of the antiemetic effect of dexamethasone is not fully understood it was suggested that dexamethasone may change in the permeability of the blood-brain barrier to serum proteins, inhibit of endogenous opioid release and central prostaglandin synthesis [15,16].

In one study, a single dose of glucocorticoid was given at different times during the the perioperative period (perioperative period is defined as the time interval 12 hours before surgery until the end of surgery) and it was found that GC reduced postoperative pain and vomiting and nausea in all application times [17] We preferred to administration of dexamethasone at 1 minute before anesthesia and found that this application of 8 mg dexamethasone reduced postoperative rescue analgesic requirements and PONV.

Borgeat et al. [18] demonstrated that propofol in sub hypnotic doses (10 mg) possesses direct antiemetic properties in the context of minor elective surgery. Furthermore, the use of propofol for maintenance of anesthesia has a positive effect on PONV reduction [19]. Area postrema has the highest concentration of the 5 HT3 receptors in the brain. Possible stimulation of the 5 HT3 receptors in the area postrema with propofol may cause antiemetic effect. The authors found that the levels of serotonin was reduced in the area postrema and CSF in propofol administered rats. Thus, antiemetic properties of propofol may be attributed to its weak serotonin antagonistic effect [20].

Song et al. [21) administered propofol 0.5mg/kg intravenously. at the end of a surgical procedure. They found that it is effective for preventing PONV in patients undergoing LC even at this dose. On the other hand, the small dose of propofol (0.5 mg/kg) administered at the end of surgery prolonged the times to awakening and orientation, but it did not delay the time to discharge from the post anesthesia care unit [21]. The sub hypnotic dose (1 mg/kg/h) of propofol was shown to be effective for prevention nausea and vomiting in patients undergoing caesarean section under spinal anesthesia [22]. In another study, authors found that PONV was reduced significantly in the total intravenous anesthesia with propofol group compared to isoflurane-nitrous oxide anesthesia group [23].

Erdem et al. [24] used sub hypnotic propofol infusion plus dexamethasone to prevent POV in children undergoing tonsillectomy. In this study, the authors found that sub hypnotic propofol infusion added to dexamethasone is more efficient than dexamethasone alone).. Also, we demonstrated that propofol infused at a rate of 1 mg/kg/h for during of operation reduced incidence of PONV did not prolong awakening time.

Propofol used for the induction and maintenance of anesthesia effectively reduced early (0-6 h) PONV incidence in postoperative period [23].In our study, early PONV incidence was similar in dexamethasone and propofol group. So we can suggested that propofol was as effective as dexamethasone for early PONV.

In group D and group C, we infused 10 % intralipid as a placebo. Oestman et al. [25] demonstrated that intralipid have not antiemetic effect. So intralipid may be placebo for propofol, particularly in study of emesis.

Limitations of this study: Operation and anesthesia times were longer than other study. While this situation was not create a significant difference between the groups, incidence of the postoperative nausea and vomiting may be increased.

**Conclusion**

We concluded that propofol 1 mg/kg/h is as effective as dexamethasone for the prevention of PONV during the first 24 hours after anesthesia in patients undergoing LC. Furthermore, dexamethasone effectively reduced the rescue analgesic requirement, while sub hypnotic propofol infusion did not.

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**Legends:**

**Table 1: Demographic and operative characteristics of patients.**

**Table 2: Incidence of nausea and vomiting during 24 h postoperatively**

**Table 3: Analgesia (diclofenac sodium 50 mg) requirements**

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**Table 1:** Demographic and operative characteristics of patients.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Group Dexametasone** | **Group** **Propofol** | **Group** **Control** |
| **Age (years)** | 49.6±11.7 | 50.07±12.1 | 49.9±12.6 |
| **Weight (kg)** | 74.5±13.3 | 74.2±12.9 | 73.9±13.5 |
| **Height (cm)** | 169±9.7 | 168.1±10.5 | 168.7±10.1 |
| **Sex (M/F)** | 23/17 | 24/16 | 25/15 |
| **ASA (1/2 )** | 27/13 | 29/11 | 28/12 |
| **Smokers** | 11 | 10 | 12 |
| **Duration of surgery(min.)** | 78.5±14.2 | 77±13.9 | 80.2±14.4 |
| **Duration of anesthesia (min.)** | 101.8±9.5 | 99.9±10.5 | 98.7±11.6 |
| **Fentanly administered(µg)** | 173.1±55.2 | 169.3±55.8 | 170.6±53.9 |
| **Awakening time (min.)** | 5.9±1.24 | 6.2±1.21 | 6.1±1.2 |

Values are n or mean ± standard deviation. ASA: American Society of Anesthesiologists classification

**Table 2: Incidence of nausea and vomiting during 24 h postoperatively**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Group Dexametasone****(n=40)** | **Group** **Propofol****(n=40)** | **Group** **Control****(n=40)** |
| **0-6 hours**1. **none**
2. **Nausea**
3. **Nausea with request for antiemetics**
4. **Vomiting**

**Total PONV****Rescue antiemetic** | 28 (70%)8(20%)4(1%)012(30%)4 | 27(67.5%)6(15%)2(5%)4(10%)12(30%)4 | 14(35%)12(30%)10**4****26(65%)\*#****13\*#** |
| **6-12 hours**1. **none**
2. **Nausea**
3. **Nausea with request for antiemetics**
4. **Vomiting**

**Total PONV****Rescue antiemetic** | 32(80%)8(20%)008(20%)1 | 29(72.5%)10(25%)0010(25%)3 | 1913**2****6****21(52.5%)\*#****8\*** |
| **12-24 hours**1. **None**
2. **Nausea**
3. **Nausea with request for antiemetics**
4. **Vomiting**

**Total PONV****Rescue antiemetic** | 36(90%)4(10%)004(10%)0 | 31(77.5%)7(17.5%)1(2.5%)08(20%)1 | 22(55%)16(40%)02(5%)**18(45%)\*#**3 |
| **0-24 hours****Total PONV** | **15(37.5%)** | **16(40%)** | **29(72.5%)\*#** |

**\* compared with Group D p<0.05 # compared with Group P p<0.05**

**Table 3: Analgesia (diclofenac sodium 50 mg) requirements**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Group D | Group P | Group C |
| **Diclofenac sodium Requirements (patients no)**  | 2(5%)  | 3(7.5%)  | 8(20%)***\**** |

\*p<0.05 compared with group D.