Original Article

Preventive Effect of Paracetamol and Dexamethasone on Nausea, Vomiting, and Pain after Laparoscopic Cholecystectomy

Reihanak Talakoub[1*], Gholam Reza Khalili[1], Babak Haghanifar[1]

Abstract

Background: The currently used antiemetic drugs are not effective in all post-operative patients due to multifactorial origin of nausea and vomiting. Therefore, the present study was designed to evaluate the preventive effect of paracetamol on postoperative nausea and vomiting (PONV) in comparison with dexamethasone in patients undergoing elective laparoscopic cholecystectomy.

Materials and Methods: in this double-blinded clinical trial 105 patients were selected using a random sampling method; they were American standards association (ASA) class I and II, 18-75 years and candidate for laparoscopic cholecystectomy; randomly assigned into three groups: Paracetamol, Dexamethasone, and control. They were anesthetized using the same method, using sodium thiopental, Fentanyl, Atracurium, and Lidocaine. Anesthesia was maintained with oxygen, Isoflurane and Morphine. They also received 6 mL/kg/h ringer lactate. Patients data were recorded and analyzed.

Results: The mean severity of nausea and vomiting in the recovery room at minutes 30, 45, and 60 had a significant difference between the groups ($p<0.05$). The satisfaction score at minutes 45 and 60 had a significant difference between the groups ($p<0.05$). However, the mean scores of satisfaction of patients at 15 and 30 minutes were almost the same and no significant difference between the three groups was reported ($p>0.05$).

Conclusion: The severity of nausea and vomiting was low in the Paracetamol group and Paracetamol was more effective than Dexamethasone in terms of reducing the rate of nausea and vomiting.

Keywords: Paracetamol, Dexamethasone, laparoscopic cholecystectomy

Please cite this article as: Talakoub R, Khalili GR, Haghanifar B. Preventive Effect of Paracetamol and Dexamethasone on Nausea, Vomiting, and Pain after Laparoscopic Cholecystectomy under General Anesthesia and its Comparison with Controls. J Cell Mol Anesth. 2018;3(3):114-21.

1-Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding Author: Reihanak Talakoub Associate Professor, Anesthesiology Department, Alzahra Hospital, Soffeh Blvd, Isfahan, Iran.
Tel/Fax: +98-31-3620-2020
Email: Reihanak.Talakoub@gmail.com

Introduction

Laparoscopic cholecystectomy (LC) is a gold standard surgical procedure for cholelithiasis and some cases of cholecystitis and gallbladder stone. Although the surgical techniques are improved and have satisfied outcomes, postoperative nausea and vomiting (PONV) is a common and disturbing effect arisen from operation and anesthesia and is often more irritating than surgical pain. The prevalence of PONV depends on many factors including anesthesia type, length and type of operation, and patient gender since women develop PONV more than men do. Patients with motion sickness are more affected by

PONV. Routine use of antiemetic drugs is not required in all surgeries because according to statistics, 30% of patients develop this effect after surgery.

Patients undergoing laparoscopic cholecystectomy (LC) are more prone to PONV with a reported occurrence of 53-72%, and this increases the length of recovery, the delay in patient discharge, patient dissatisfaction, and hospital costs. The reason for LC-induced PONV is not clear yet, however, some factors are involved such as using isoflurane and fentanyl during operation, peritoneum stretching, increased blood pressure in the peritoneal cavity, and narcotics injection after operation.

Different efforts have been done to reduce the occurrence of PONV, and many antiemetic drugs have been studied. However, given the multifactorial origin of PONV, these medicines are not completely effective in all patients. Meanwhile, Dexamethasone is used as an effective antiemetic drug, which mechanism has not been understood, but it may act through central inhibition of prostaglandin synthesis, serotonin inhibition in intestine, inhibition of endorphin release, and change in permeability of blood brain barrier to serum proteins (1-3). Various studies have investigated the impact of Dexamethasone alone or in combination with other medicines on PONV.

In a double-blinded randomized clinical trial in 2009, Fuji *et al.* studied the effect of Dexamethasone in reducing nausea, vomiting, and the need for analgesics after operation. In this study, 90 patients who were candidate for LC were divided into three groups of Dexamethasone 8 mg, Dexamethasone 4 mg, and placebo, and were evaluated in terms of nausea, vomiting, and the need for analgesics after operation. Finally, it was concluded that dexamethasone 8 mg is effective in reducing nausea, vomiting, and the need for analgesics after operation in patients undergoing LC (4).

Sanchez-Rodriguez *et al.* (2010) investigated the preventive effect of Dexamethasone on PONV in a double-blinded randomized clinical trial. They divided 210 patients elected for LC into two groups of 8 mg dexamethasone and placebo. The results showed that the pharmaceutical regimen used was safe with no specific adverse effect and significantly reduced PONV in patients undergoing LC (5). Intravenous paracetamol or acetaminophen is other drug studied for reducing nausea and vomiting.

Intravenous Paracetamol or Acetaminophen is widely used as an analgesic and despite its known little anti-inflammatory and anti-pyretic effects; it has sufficient impact on peripheral and central pain systems (12). It acts through inhibitory mechanism of bradykinin in the peripheral system and through mediators such as NMDA, substance P, and nitric oxide pathway in the central system (6, 7).

In 2011, Cok *et al.* studied the effect of Paracetamol on PONV. A total of 90 patients of 2 to 14 years old undergoing strabismus surgery were divided into two groups of Paracetamol (15 mg/kg) and normal saline and were evaluated in terms of postoperative nausea and vomiting and the need for analgesics. The results showed that Paracetamol significantly reduced postoperative nausea and vomiting and the need for analgesics in the first 24 hours (8).

The objective in the present study was to prevent this condition, and most studies address this issue rather than treatment. Review of the literature showed that previous studies have investigated the effects of Paracetamol and Dexamethasone on PONV individually in comparison with placebo, however, no study was found regarding the comparison of Paracetamol and Dexamethasone. Therefore, this study was designed to compare the effect of Paracetamol and Dexamethasone on PONV in patients electively undergoing laparoscopic cholecystectomy.

Methods

This double-blinded clinical trial was performed in Al-Zahra Medical Center of Isfahan in 2014-2015, after obtaining permits from the ethics committee of the university and informed consent of patients. A total of 105 men and women ASA (I, II) aging from 18 to 75 years who were candidate for laparoscopic cholecystectomy under general anesthesia were randomly divided into three groups.

Exclusion criteria: history of drug addiction and long-term use of oral sedatives or analgesics, history of motion sickness, pregnancy, previous heart or lung disease, liver, kidney, or thyroid dysfunction,

investigational drug intake within 30 days before surgery, nausea and vomiting or the use of antiemetic or H2 blockers within 48 hours before surgery, history of sensitivity to dexamethasone and paracetamol (in the case of drug sensitivity, severe hemodynamic impairment more than 30% of the baseline lasting more than 15 minutes), patients requiring transfusion, changing laparoscopic surgery to open surgery, and changing anesthesia method or the anesthetic drugs.

All patients were nil per os (NPO) for at least 8 hours and received 1/3-2/3 serum according to "1-2-4 rule of thumb". Patients were anesthetized with a completely similar method. To induce anesthesia, they received Thiopental sodium (6 mg/kg), Fentanyl (2 µg/kg), Atracurium (0.6 mg/kg), and Lidocaine (1.5 mg/kg). Anesthesia was continued with oxygen (6 L/min), Isoflurane (1.2-1.8%), and Morphine (0.15 mg/kg). They also received 6 mL/kg/h ringer lactate.

The patients selected through the simple randomized sampling method were divided into three groups.

Paracetamol group received 15 mg/kg intravenous Paracetamol in 15 minutes before closing the wound within a micro-set with 100 mL normal saline through infusion and 2 mL normal saline through intravenous injection. Dexamethasone group received 100 mL normal saline within 15 minutes before closing the wound through infusion and 8 mg dexamethasone (2 mL) through intravenous injection. Placebo group received 100 mL normal saline within 15 minutes before closing the wound through infusion and 2 mL normal saline through intravenous injection.

During anesthesia, mean arterial pressure, mean end-expiratory CO_2/SpO_2, and heart rate were monitored. All information including age, gender, weight, length of anesthesia and surgery, length of stay in the recovery room, length of extubating, nausea severity, vomiting frequency, and satisfaction scores were recorded. Mean arterial pressure and heart rate were measured before anesthesia and every 30 minutes during the operation. Bradycardia (heart rate <50 per min) was treated with 1 mg IV atropine.

At the end of operation, occurrence of nausea and vomiting, frequency of vomiting and severity of nausea were recorded and scored based on VAS; then, ranked from 0 to 10: zero for no nausea and 10 standing for unbearable vomiting. Also, vomiting scored from 0 to 3 (0 = no vomiting, 1 = 1 time vomiting, 2 = 2 times vomiting, and 3 = 3 or more times vomiting); retching equivalent to vomiting.

If the nausea score was 4 or higher and vomiting score was 3 or higher, 4 mg Ondansetron was slowly injected intravenously. The first time for receiving Ondansetron and the total received of that in 24 hours were recorded. The incidence of nausea and vomiting and the vomiting frequency were also recorded up to 24 hours. Pain intensity was scored using VAS from 0 to 10. If the pain score was 4 or greater, fentanyl (0.5 mg/kg) was administered.

The time of pethidine painkiller request, *i.e.* the time between surgery and the first dose of analgesic given at the request (VAS >4) and the total dose of consumed analgesic after 24 h were calculated and recorded. Postoperative VAS was recorded at minutes 15, 30, 45, and 60 in the recovery and at hours 6, 12, 24. Satisfaction was scored from 1 to 4 (1 = mild, 2 = moderate, 3 = good, 4 = excellent). Sedation level in the recovery room was evaluated and recorded at minutes 15, 30, 45, and 60 through Kulka method.

The Kulka method for evaluation of sedation: 0=Awake, 1=Drowsy or calm waking up easily, 2=Drowsy responding quick to verbal stimulation, 3=Drowsy responding late to verbal stimulation, 4=Unconsciousness, Criteria for discharging from recovery room was based on the modified Aldrete score (1). After collecting and completing, the data were analyzed using SPSS® software version 18 (SPSS Inc., Chicago, Ill., USA).

Results

Similar letters indicated no significant differences between the means according to Duncan's post hoc test (table 1). The mean severity of nausea at 6 hours after surgery had a significant difference between the three groups (p<0.05). However, the mean severity of nausea at 12 and 24 hours were almost identical between the three groups and had no significant difference (p >0.05). Using Duncan's post hoc test, the mean severity of nausea was also compared between the three groups two by two. Based of Duncan's test, the highest and the lowest mean of nausea severity at 6 hours were seen in the control group and in the paracetamol group,

respectively.

Similar letters indicate no significant differences between the means according to Duncan's post hoc test (table 2). The mean patient satisfaction score at 6, 12 and 24 hours after surgery had significant differences between the three groups (p<0.05). Using Duncan's post hoc test, the mean severity of nausea was also compared between the three groups two by two. Based of Duncan's test, the highest and the lowest mean of patients satisfaction score were seen in the dexamethasone group and in the control group, respectively.

In table 3, the frequency of vomiting was compared between the three groups using Chi-square test at every step of measuring. The significance level of this test for 6 hours after surgery was calculated less than 0.05. Therefore, the vomiting rate at 6 hours after surgery had a significant difference between the three groups, but no significant difference existed at 12 and 24 hours after surgery. It can be seen that the vomiting rate at 6 hours after surgery was higher in the control group than other groups (the severity percent of vomiting 0 was higher in other groups than the controls). The vomiting rate at 6 hours after surgery was higher in the dexamethasone group than the paracetamol group (the severity percent of vomiting 0 in the Paracetamol group was higher than the Dexamethasone).

Similar letters indicate no significant differences between the means according to Duncan's post hoc test (table 4). The mean time of the first narcotic request had significant differences between the three groups (p<0.05). In the control group, the narcotic was requested approximately 2 hours earlier than the Dexamethasone group and in the Dexamethasone group almost 1 hour earlier than Paracetamol group.

The frequency of sedation level was compared between the three groups using Chi-square test at every step of measuring. The significance level of this test for different minutes was calculated less than 0.05. Therefore, the sedation level at these minutes had a significant difference between the three groups. It was observed that the sedation levels at minutes 15, 30, 45 and 60 in the recovery room were higher in the control and Dexamethasone groups than the Paracetamol group. In other words, the rate of sedation levels 3 and 4 in the control and Dexamethasone groups was higher than the Paracetamol group and the rate of sedation levels 0 and 1 in the Paracetamol group was higher than the control and Dexamethasone groups.

Similar letters indicate no significant differences between the means according to Duncan's post hoc test (table 5). The pain scores at 6 and 12 hours after surgery had significant differences between the three groups (p<0.05). The mean pain intensity at 24 hours after surgery was nearly identical between the groups and had no significant difference (p>0.05). Using Duncan's post hoc test, the mean pain intensity was also compared between the three groups two by two. Based of Duncan's test, the highest and the lowest mean of pain intensity at 6 and 12 hours after operation were seen in the control group and in the Paracetamol group, respectively. In other words, postoperative pain was lower in Paracetamol group than other groups.

Results showed that the mean arterial blood pressure during surgery was nearly identical between the three groups and had no significant difference (p>0.05). The mean arterial blood pressure measured every 30 minutes in the recovery room was almost identical between the three groups and there was no significant difference (p>0.05). Although the lowest mean arterial blood pressure at different times was seen in the dexamethasone group, this decline was not statistically significant.

The mean heart rate during surgery were significantly different between the three groups (p<0.05). According to Duncan's test, the maximum heart rate during surgery was seen in the paracetamol group and lowest in the dexamethasone group. The mean heart rate measured every 30 minutes in the recovery room was almost identical in the three groups and there was no significant difference (p>0.05). The lowest mean heart rate at different times was seen in the dexamethasone group, but this reduction was not statistically significant.

Discussion

Difference in pain intensity among the groups was a result obtained in this study. The results indicated that pain intensity was lower in the paracetamol group, while the findings of Waldron *et*

al. in 2013 were in contrast with ours. They stated that pain was lower in the dexamethasone group (9). However, Karnak *et al.* reported findings similar to ours. Pain intensity was lower in the paracetamol group (10). This difference may be attributed to this fact that Waldron *et al.* performed a systematic review and meta-analysis including 5796 patients.

Patient satisfaction and sedation level, both higher in the dexamethasone group than in other groups, were other results obtained by this study. In this regard, a number of similar findings have been reported. For example, Chan *et al.* (2014) stated the higher satisfaction of patients in the dexamethasone group (11). In 2016, Jessen *et al.* reported a higher level of sedation and satisfaction in the dexamethasone group (12).

In this study, the groups were also compared in terms of heart rate during surgery, and it was observed that the maximum heart rate during surgery was seen in the paracetamol and the lowest in the dexamethasone group. In this case, Powell *et al.* (2016) reported findings similar to ours. They stated that the lowest heart rate during operation had a significant relationship with dexamethasone injection (13).

Difference in nausea severity and vomiting rate among groups was another result in this study. According to our findings, both cases were lower in the paracetamol group. While Guay *et al.* (2016) reported contrary findings (14). However, in 2016, Zou *et al.* provided findings similar to ours. They also confirmed low level and severity of nausea in the paracetamol group (15). According to differences in the results in one year and different sample size, it is recommended to perform the future studies with higher sample size to could make decisions that are more confident.

Conclusion

In this study, the effect of paracetamol on post-operative nausea and vomiting (PONV) and pain was compared with dexamethasone in patients who underwent elective laparoscopic cholecystectomy, and it was found that the severity of nausea and vomiting was lower in the paracetamol group, and paracetamol was more effective in reducing the rate of nausea and vomiting. In contrast, patient satisfaction and sedation level between the studied groups was higher in the dexamethasone group than other groups.

Acknowledgment

The authors appreciate the kind help of all physicians and nurse, Al-Zahra Medical Center Isfahan, Iran.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Aapro ms,Albert Ds. Dexamethasone as an antiemetic in patients treated with ciplatin. N Engl J Med. 1981;305:520.
2. Rich WM, Abdulhayoglu G, DiSaia PJ.Methylprednisolone as an antiemetic during cancer chemotherapy – a pilot study. Gynecol Oncol. 1980;9:193–8.
3. Fredrikson M, Hursti T, Furst CJ. Nausea in cancer chemotherapy is inversely related to urinary cortisol excretion. Br J Cancer. 1992;65:779 80.
4. Harris AL. Cytotoxic-therapy-induced vomiting is mediated via enkephalin pathways. Lancet. 1982;1:714–6.
5. Elhakim M, Ali NM, Rashed I, Riad MK, Refat M. Dexamethasone reduces postoperative vomiting and pain after pediatric tonsillectomy. Can J Anaesth. 2003;50 (4):392-7.
6. Bianchin A, De Luca A, Caminiti A. Postoperative vomiting reduction after laparoscopic cholecystectomy with single dose of dexamethasone. Minerva Anestesiol. 2007;73(6):343-6.
7. Fujii Y, Itakura M. Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2010;24(3):692-6.
8. Fukami Y, Terasaki M, Okamoto Y, Sakaguchi K, Murata T, Ohkubo M, Nishimae K. Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy. J Hepatobiliary Pancreat Surg. 2009;16(3):367-71.
9. Waldron NH1, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110(2):191-200.
10.Kranke P1, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LH, Poepping DM, Weibel S. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev. 2015;(7):CD009642.
11.Chan EY1, Fransen M, Parker DA, Assam PN, Chua N. Femoral nerve blocks for acute postoperative pain after knee replacement surgery. Cochrane Database Syst Rev. 2014;(5):CD009941.
12. Jessen Lundorf L1, Korvenius Nedergaard H, Møller AM. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. Cochrane Database Syst Rev. 2016; 2:CD010358.
13.Powell R1, Scott NW, Manyande A, Bruce J, Vögele C, Byrne-Davis LM, Unsworth M, Osmer C, Johnston M. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database Syst Rev. 2016 ;(5):CD008646.
14.Guay J1, Nishimori M, Kopp S. Epidural local anaesthetics

versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting and pain after abdominal surgery. Cochrane Database Syst Rev. 2016;7:CD001893.

15.Zou Z1, An MM, Xie Q, Chen XY, Zhang H, Liu GJ, Shi XY. Single dose intra-articular morphine for pain control after knee arthroscopy. Cochrane Database Syst Rev. 2016;(5):CD008918.

Table 1: Comparison of the mean severity of nausea in three groups at 6, 12, and 24 hours postoperatively

Severity of Nausea	**Groups**	**Mean**	**Standard deviation**	***p*-value**
at 6 hours after operation	Control	0.8890a	0.51400	0.037
	Paracetamol	0.0010c	0.61400	
	Dexamethasone	0.1814b	1.01400	
at 12 hours after operation	Control	0.4929a	1.30094	0.094
	Paracetamol	0.1120a	0.01400	
	Dexamethasone	0.4857a	1.62956	
at 24 hours after operation	Control	1.5714a	1.44070	0.736
	Paracetamol	1.1714a	1.01419	
	Dexamethasone	1.3429a	1.57074	

Table 2: Comparison of the mean patient satisfaction score at 6, 12 and 24 hours after surgery in three groups

		Mean	Standard deviation	*p*-value
Satisfaction at 6 hours after operation	Control	1.9333c	1.00491	0.044
	Paracetamol	2.8286b	1.0008	
	Dexamethasone	3.5455a	1.67801	
Satisfaction at 12 hours after operation	Control	1.0000c	1.20015	0.035
	Paracetamol	2.7143b	1.90867	
	Dexamethasone	3.4138a	2.00922	
Satisfaction at 24 hours after operation	Control	1.7813c	1.28852	0.015
	Paracetamol	2.8571b	0.64820	
	Dexamethasone	3.7576c	2.15102	

Table 3: Frequency distribution of vomiting rate at 6, 12, and 24 hours after surgery in three groups

		6 hours after operation	**12 hours after operation**	**24 hours after operation**
Group	Vomiting rate	Frequency (%)	Frequency (%)	Frequency (%)
	0	27 (77.1%)	28 (80.0%)	32 (91.4%)
Control	1	8 (22.9%)	6 (17.1%)	3 (8.6%)
	2	0 (0.0)	1 (2.9%)	0 (0.0%)
	0	35 (100%)	٣٤ (97.1%)	35 (100%)
Paracetamol	1	0 (0.0%)	1 (2.9%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	0	28 (82.4%)	27 (77.1%)	35 (100%)
Dexamethasone	1	6 (17.6%)	8 (22.9%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0)	0 (0.0%)
Chi-square test		8.608	8.166	6.176
Significance level		0.014	0.0٨٦	0.05٦

Table 4: Comparison of the mean narcotic consumption during 24 hours in three group

Groups	**Mean**	**Standard deviation**	***p*-value**
Control	2.3333c	1.51866	
Paracetamol	5.5500a	1.36660	0.041
Dexamethasone	4.5625b	1.96600	

Table 5: Comparison of the mean pain intensity at 6, 12, and 24 hours postoperatively in three groups

Pain Severity		**Mean**	**Standard deviation**	***p*-value**
At 6 hours postoperatively	Control	1.4600a	1.98820	0.045
	Paracetamol	0.4671b	1.37932	
	Dexamethasone	1.4743a	1.92157	
At 12 hours postoperatively	Control	2.4691a	2.16038	0.000
	Paracetamol	0.4299b	0.88403	
	Dexamethasone	1.7509a	1.52128	
At 24 hours postoperatively	Control	0.0580a	0.16903	0.145
	Paracetamol	0.0289a	0.33806	
	Dexamethasone	0.2871a	0.95706	