Effect of single dose preemptive intravenous paracetamol, dexamethasone, and magnesium sulfate on perioperative hemodynamic variables and post-operative nausea, vomiting, and pain in open cholecystectomy done under general anesthesia: A prospective, randomized, and single-blind study

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ABSTRACT

Background: Pain due to open cholecystectomy can result in delayed recovery and poor operative outcomes. Multimodal approaches to pain control cause functional improvement. We compared the efficacy of paracetamol 1 g, dexamethasone 8 mg, and magnesium sulfate 2 g with normal saline in control over perioperative hemodynamics and post-operative pain in patients undergoing open cholecystectomy under general anesthesia. **Aims and Objectives:** This study conducted to assess the effect of preemptive intravenous paracetamol, dexamethasone, and magnesium sulfate on perioperative hemodynamic variables (primary outcome) and post-operative nausea, vomiting, and pain (secondary outcome) in open cholecystectomy. **Materials and Methods:** Sixty patients of ASA Grade I/II were randomized into two groups to receive either normal saline 100 ml iv (Group C, n = 30) or infusion containing inj. paracetamol 1 g, inj. dexamethasone 8 mg and inj. magnesium sulfate 2 g iv (group PDM, n = 30), 20 min before induction. Intraoperative and post-operative hemodynamic data, post-operative pain scores, and incidence of nausea vomiting were recorded. **Results:** Intraoperative pulse rate was significantly higher at intubation and 15 min after intubation in the control group and intraoperative systolic, diastolic, and mean arterial blood pressure were significantly higher in control group at intubation and until 60 min. Post-operative pulse rate was significantly higher in the control groups at 180 min and incidence of PONV reduced in PDM group until 90 min. **Conclusion:** Preemptive intravenous infusion of paracetamol, dexamethasone, and magnesium sulfate provided better stability over perioperative hemodynamics, reduced the incidence of post-operative nausea vomiting, and provided better post-operative pain control.

Key words: Paracetamol; Dexamethasone; Magnesium sulfate; Perioperative hemodynamics; Pain

INTRODUCTION

The incidence of gallstones has been increasing recently due to which cholecystectomy has become a very common surgery. Laparoscopic cholecystectomy is preferred nowadays, but due to longer operative time, increased incidence of biliary leakage, difficult surgical procedure due to intense inflammation or scarring of gall bladder,

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excessive bleeding, or stones in the bile duct, open cholecystectomy is often required.[1] Pain management in open cholecystectomy poses a big challenge to the anesthesiologist and single drug for pain control failed to show satisfactory results. Therefore, a multimodal approach for pain control has been used widely.[2] Once the central sensitization of noxious stimuli occurs, it is difficult to control pain and the requirement of recue analgesics also increases. Preemptive analgesia is the intervention done to prevent the central sensitization of noxious stimuli.[2] Paracetamol, an acetaminophen product, acts through activation of descending serotonergic inhibitory pathways and through the inhibition of prostaglandins by producing cyclooxygenase (COX-1), COX-2 and COX-3 inhibition, thereby providing adequate perioperative analgesia for mild-to-moderate pain.[3,4] Dexamethasone, a strong long acting glucocorticoid, by inhibiting the peripheral phospholipase causes a decrease in the COX and lipooxygenase production aiding in reducing inflammation, pain, and post-operative nausea vomiting, thus enhancing the recovery process.[5,6] Magnesium sulfate, an antagonist of NMDA receptor, suppresses the passage of electrical currents through membranes by suppressing the mentioned receptors.[7] Administration of magnesium sulfate prevents the induction of central sensitization after a peripheral nociceptive stimulus and has been shown to reduce intra operative analgesic requirements and post-operative pain.[8,9]

On the literature search, we could not find any research paper on the combined use of paracetamol, magnesium sulfate and dexamethasone in general anesthesia for open cholecystectomy. Hence, this study evaluated the combined effects of paracetamol, magnesium sulfate, and dexamethasone administration as multimodal analgesia on perioperative hemodynamic variables (primary outcome) and post-operative nausea, vomiting, pain relief, and analgesic requirement (secondary outcome) in patients who underwent open cholecystectomy under general anesthesia.

Aims and objectives

This study was conducted to assess the effect of preemptive intravenous paracetamol, dexamethasone, and magnesium sulfate on perioperative hemodynamic variables (primary outcome) and post-operative nausea, vomiting, and pain (secondary outcome) in open cholecystectomy.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, the present prospective, single blinded, randomized, and controlled study was carried out on patients aged 20–40 years of ASA Grade I and II, scheduled for open cholecystectomy. No formal sample size calculation was done and a convenient sampling was done to examine a total of 60 patients. Patients who refused to participate, uncooperative, weighed >60 kg, pregnant or lactating, had any history of significant pulmonary, cardiovascular, neurological, hepatorenal, psychiatric, metabolic disease, or bleeding diathesis were excluded from the study.

After obtaining informed consent, all the patients were examined a day before surgery to do complete general, physical, and systemic examination. All the required routine and special investigations as per hospital protocol including complete blood count, random blood sugar, blood urea, serum creatinine, E.C.G., and chest X-ray were carried out.

All patients were kept nil orally for at least 6 h before the procedure.

Patients were randomly divided by sealed envelope method into two groups by the anesthesiologist and the patients were blinded to the drug they received (single-blinded study).

Group PDM (n=30) received intravenous infusion of paracetamol (1 g), inj.dexamethasone (8 mg) and inj. magnesium sulfate (2 g) in 100 ml bottle, 20 min before induction.

Group C (n=30) received 100 ml normal saline intravenously 20 min before induction. Both the groups received inj. pentazocine 0.5 mg/kg during pre-oxygenation to minimize the hemodynamic responses.

On arrival of the patient in operation theater, all routine monitors including pulse oximeter non-invasive blood pressure cuff and E.C.G were connected and observations were recorded. All the baseline (B0) vital parameters including – basal pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure, and oxygen saturation were recorded. An intravenous access was achieved with 18 G cannula in the patient's forearm. All the patients received inj. glycopyrrolate 0.02 mg iv slowly, inj. metoclopramide 10 mg iv, and inj. ondansetron 8 mg iv as premedication.

During pre-oxygenation, inj. pentazocine 0.5 mg/kg was administered in every patient for preemptive analgesia. General anesthesia was induced with inj.propofol 2.5 mg/kg. Endotracheal intubation was done with appropriate size ETT with inj succinylcholine 2 mg/kg. Anesthesia was maintained on nitrous oxide + oxygen (66:33) along with isoflurane (0.5 MAC) to prevent awareness and inj. atracurium as loading (0.25 mg/kg) and maintenance doses (0.1 mg/kg). At the end of the procedure, 0.5% ropivacaine
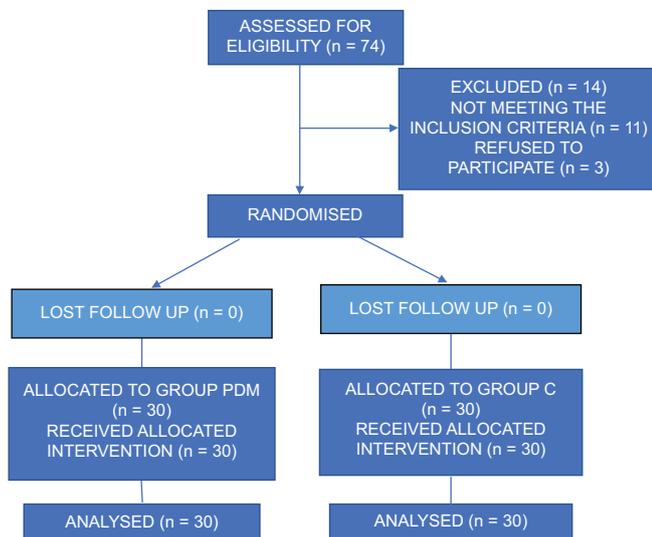
(20 ml) was infiltrated diffusely over the incisional line and deeper layers to prevent early onset of post-operative pain. Patients were reversed with inj. neostigmine (0.04–0.08 mg/kg) + glycopyrrolate (0.005–0.01 mg/kg). All the patients were shifted to the recovery room for further monitoring and evaluation.

SBP, DBP, mean arterial blood pressure (MAP), heart rate, and oxygen saturation were recorded intraoperatively by the anesthesiologist at 15 min interval in the first 60 min and then at 90 min and in post-operative period at 30 min interval in the first 120 min and then at 180 min. Post-operative pain was assessed by visual analog scale (VAS) scoring. Moderate-to-severe pain (VAS score >3) was treated with inj.tramadol 2 mg/kg intravenously. Nausea, vomiting, and shivering were recorded if present in the post-operative period. Vomiting episodes were treated with inj. ondansetron 8 mg intravenously.

Statistical analysis

Obtained data were composed in suitable spreadsheet, that is, EXCEL and SPSS. Statistical analysis was carried out using independent t-test, Chi-square test, and Mann–Whitney-U-test. Significance level will be 95% confidence level (P<0.05).

Consort chart

ASSESSED FOR ELIGIBILITY (n = 74)

EXCLUDED (n = 14) NOT MEETING THE INCLUSION CRITERIA (n = 11) REFUSED TO PARTICIPATE (n = 3)

RANDOMISED

LOST FOLLOW UP (n = 0)

LOST FOLLOW UP (n = 0)

ALLOCATED TO GROUP PDM (n = 30) RECEIVED ALLOCATED INTERVENTION (n = 30)

ALLOCATED TO GROUP C (n = 30) RECEIVED ALLOCATED INTERVENTION (n = 30)

ANALYSED (n = 30)

ANALYSED (n = 30)

RESULTS

Both the study groups were comparable as regards to demographic data (age, sex, and weight) as shown in Table 1.

- On comparing both the groups intraoperative pulse rate was significantly higher at intubation (96.7 – Group C, 84.7 – Group PDM; P=0.001) and 15 min

after intubation (88.0 – Group C, 81.2 – Group PDM; P=0.048) in the control group (Graph 1).
- Intraoperative SBP (mmHg) was significantly higher (P<0.05) in control group at intubation, after 15, 30, 45, and 60 min (Table 2).
- Intraoperative DBP (mmHg) was significantly higher (P<0.05) in control group at intubation, after 15, 30, and 45 min (Table 2).
- Intraoperative MAP (mmHg) was significantly higher (P<0.05) in control group at induction, after 15, 30, and 45 min (Table 2).
- Intragroup comparison of SBP changes showed statistically significant changes (P<0.05) at induction, intubation, after 15, 30, 45, 60, and 90 min in Group C where as in Group PDM, there was a statistically significant decrease (P=0.012) at induction (Table 3).
- Intragroup comparison of DBP and MAP changes showed statistically significant (P<0.05) changes at induction, intubation, after 15, 30, and 45 min in Group C where as in Group PDM, statistically significant increase was observed at intubation only (Table 3).
- Post-operative pulse rate was significantly higher (P=0.03) in the control group at 180 min.
- Incidence of PONV was found to be decreased in Group PDM as compared to Group C at 30, 60, and 90-min postoperatively (Table 4).
- Post-operative pain was significantly decreased (P=0.0001) in the PDM group at 30 min, 60 min, 90 min, 120 min, and 180 min postoperatively (Table 4).
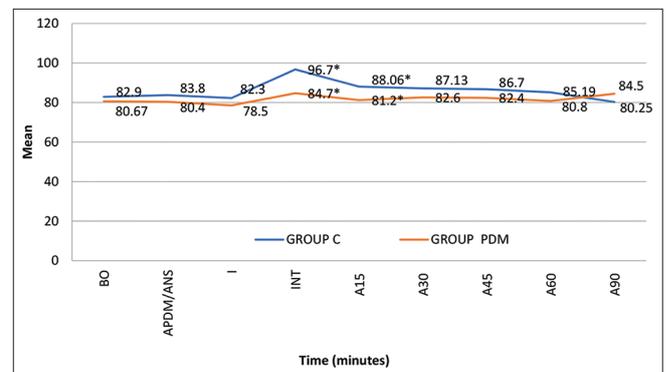
Graph 1: Comparison of pulse rate (BPM) at different time intervals in both the study groups. *Significant difference, **Highly significant difference, BO: Baseline, APDM: After PDM, ANS: After NS, I: Induction, INT: Intubation, A15, A30, A45, A60, and A90 – after 15, 30, 45, 60, and 90 min of intubation

Table 1: Demographic profile			
Parameters	**Group PDM (n=30)**	**Group c (n=30)**	**P-value**
Age (years)	33.9±5.2	33.4±6.7	0.75
Male	28 (93.3%)	28 (93.3%)	1.0
Female	2 (6.6%)	2 (6.6%)	
Weight (kg)	49±4.6	48.63±3.1	0.56

Table 2: Intergroup comparison of systolic, diastolic, and mean arterial blood pressure

Time (minutes)	SBP Mean±SD			DBP Mean±SD			MAP Mean±SD		
	Group C	Group PDM	P-value	Group C	Group PDM	P-value	Group C	Group PDM	P-value
BO	122.3±14.8	123.2±13.6	0.801	78.5±10.2	77.8±9.9	0.80	92.3±8.7	93±9.3	0.74
APDM/ANS	121.3±13.8	123.5±12.4	0.521	77.9±9.5	79.2±9.4	0.59	92.2±7.7	94.1±8.8	0.39
I	115.6±15	120±13.8	0.233	74.2±10.7	79.4±10.6	0.07	87.7±10.6	93.1±10.3	0.09
INT	138.0±11.6	122.5±12.2	0.0001**	95.1±9.2	81.4±11.2	0.0001**	108.5±10.4	95.1±10.2	0.0001**
A15	124.4±16.4	122.8±12.8	0.0001**	94.5±8.4	80.7±10.5	0.0001**	105.6±9.3	94.7±10.3	0.0001**
A30	136.0±11.9	123.3±11.5	0.0001**	95.4±6.9	79.7±9.9	0.0001**	104.2±7.7	94.3±8.9	0.0001**
A45	136.4±14.2	123.3±11.2	0.0001**	91.4±5.9	79.1±9.6	0.0001**	104.2±8.1	93.9±8.4	0.0001**
A60	135.7±12.9	122.9±11.6	0.0001**	80.9±7	78.7±9.6	0.55	93.9±6.6	93.5±8.2	0.87
A90	137.9±11.8	121.7±12.6	0.658	81.2±6.7	78.7±10.9	0.77	90.5±5.4	94.5±10.4	0.51

**Highly significant difference, APDM: After PDM, ANS: After NS, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure

Table 3: Intragroup comparison of systolic, diastolic, and mean arterial blood pressure

Time (minutes)	SBP Mean±SD		DBP Mean±SD		MAP Mean±SD	
	Group C	Group PDM	Group C	Group PDM	Group C	Group PDM
BO	122.3±14.8	123.2±13.6	78.5±10.2	77.8±9.9	92.3±8.7	93±9.3
APDM/ANS	121.3±13.8	123.5±12.4	77.9±9.5	79.2±9.4	92.2±7.7	94±8.8
I	115.6±15**	120±13.8*	74.2±10.7*	79.4±10.6	87.7±10.6*	93.1±10.3
INT	138.0±11.6**	122.5±12.2	95.1±9.2**	81.4±11.2*	108.5±10.5**	95.1±10.2*
A15	124.4±16.4**	122.83±12.8	94.5±8.4**	80.7±10.5	105.6±9.4**	94.7±10.3
A30	136.0±11.9**	123.3±11.5	95.4±6.9**	79.7±9.9	104.2±7.7**	94.3±8.9
A45	136.4±14**	123.3±11.2	91.4±5.9**	79.1±9.6	104.2±8.1**	93.9±8.4
A60	135.7±12**	122.9±11.6	80.9±7	78.7±9.6	93.9±6.6	93.5±8.2
A90	137.9±11.8*	121.7±12.6	81.2±6.7	78.7±10.9	90.5±5.4	94.5±10.4

*Statistically significant difference, **Highly significant difference, APDM: After PDM, ANS: After NS, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure

Table 4: Comparison of post-operative nausea, vomiting, and VAS scores in both the study groups

Time (minutes)	PONV				VAS scores median (IQR)		
	Group C		Group PDM				
	n	%	n	%	Group C	Group PDM	P-value
30 PO	2	6.7	0	0	3 (2-3)	1 (0-1)	0.0001**
60 PO	2	6.7	1	3.3	5 (2-7)	1 (0-1)	0.0001**
90 PO	1	3.3	0	0	6 (3-8)	1 (0-2)	0.0001**
120 PO	0	0	0	0	7 (3-8)	1 (1-2)	0.0001**
180 PO	0	0	0	0	6 (4-8)	1 (1-2)	0.0001**

**Highly significant difference, 30PO, 60PO, 90 PO, 120 PO, and 180 PO- 30, 60, 90, 120, and 180 min postoperatively

- Time for first rescue analgesia was significantly prolonged in Group PDM (375 min) as compared to Group C (101.3 min) (P=0.0001).

DISCUSSION

Post-operative pain causes anxiety, physical discomfort, limits movements, and reduces respiratory capability leading to pulmonary complications. Hence, effective control of post-operative pain not only reduces these complications but also enhances recovery and early discharge from the hospital.

In our study, demographic data were comparable in both groups (P>0.05). Both the study groups were showing female preponderance as the incidence of gall stones is higher in females.

In the present study, Inj. paracetamol 1 g, inj. magnesium sulfate 2 g, and inj. dexamethasone 8 mg given intravenously as a part of multimodal analgesia provided effective analgesia in the perioperative period (primary outcome). Arici et al.,[10] observed in his study that 1 g iv paracetamol given pre-emptively was equally effective as inj.ketamine in reducing perioperative pain. Taheri et al.,[11] found in his study that low dose iv magnesium sulfate (2 g) provided effective pain control with no side effects of high dose magnesium sulfate such as respiratory or cardiac arrest and no prolongation of action of NDMR (Low dose magnesium sulfate does not decrease the acetylcholine release from the presynaptic

membrane). Inj dexamethasone (8 mg) in addition to its analgesic effects was also found to have central antiemetic action due to activation of the glucocorticoid receptors in the bilateral nuclei tractus solitarii in the medulla.

In the intergroup comparison of intraoperative hemodynamic variables, we observed better stability in Group PDM at intubation and until 60 min after intubation as compared to Group C. A study conducted by Soltani et al.,[12] (n=80) showed significantly higher pulse rate after intubation in the saline group when compared to the paracetamol group. Ryu et al.,[13] (n=50) found significantly lower values in MAP in the magnesium sulfate group as compared to the saline group before intubation, immediately after intubation and 5 min after intubation.

In our study, it was observed that VAS scores were significantly higher in the Group C as compared to Group PDM throughout the study period. Valdivia-Sánchez and Prieto-Duarte[14] (n=92) observed a significantly higher VAS score in the control group as compared to the dexamethasone group at the 1st, 2nd, and 24th h of the post-operative period.

The time for first rescue analgesia was much higher in Group PDM as compared to Group C. Karki and Pokharel[15] (n=52) inferred that the TRA1 in the patients who received paracetamol were significantly higher than those who received diclofenac. The post-operative hemodynamic parameters (PR, SBP, DBP, and MAP) showed statistically insignificant difference when compared between the two groups at various time intervals.

Limitations of the study
There is no study available in the literature which used all the three drugs together, so we had a difficulty to compare our results with other studies.

Scope of the study
More and more studies should be conducted using a combination of paracetamol, dexamethasone, and magnesium sulfate to evaluate the effects on hemodynamic parameters, post-operative nausea, vomiting, and post-operative analgesia.

CONCLUSION

Single dose preemptive intravenous infusion of paracetamol, dexamethasone, and magnesium sulfate provided better control over perioperative hemodynamic changes. Preemptive intravenous infusion of paracetamol, dexamethasone, and magnesium sulfate reduced the incidence of post-operative nausea and vomiting and provided better post-operative pain control.

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Authors' Contributions:
DK- Concept and design of the study, reviewed the literature, and manuscript preparation; **SS-** Concept, coordination, statistical analysis and interpretation, prepared the first draft of manuscript, and interpreted the results; **UR and RS-** Revision of manuscript.

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