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Comparison of the analgesic effect of paracetamol and magnesium sulfate during and after laparoscopic cholecystectomy

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Abstract
Background and objectives: Magnesium has been proven to have antinociceptive effects which are primarily based on the regulation of calcium influx into the cell, which is natural physiological calcium antagonism and N-methyl-D-aspartate (NMDA) receptor antagonism. Multimodal analgesia, using a non-opioid analgesic in addition to an opioid analgesic, has been suggested as a way to improve postoperative pain control and reduce opioid use [1]. This study compared the analgesic effects of paracetamol and magnesium sulfate.
Methods: After taking ethical committee approval 80 patients belonging to ASA grade 1 and 2 who were planned for laparoscopic cholecystectomy surgery were randomly divided into two groups; Group 1 and Group 2. Group 1 received 15mg/kg of intravenous paracetamol and Group 2 received 20mg/kg of intravenous magnesium sulphate immediately after intubation. Pain intensities were measured and recorded using the Visual Analog Scale in the recovery room (0), 1, 3, 6, 9, 12, 18 and 24 hours after surgery.
Results: Comparatively Group 2, Group 1 patients had lower post-operative pain and consumed less analgesic drugs during first 24 hours. There is no significant variation in heart rate, systolic and diastolic pressures in both groups**.**
Conclusion: Intraoperative use of paracetamol infusion proved to produce more postoperative analgesia than with use of intravenous magnesium sulphate in laparoscopic cholecystectomy.

Keywords: Paracetamol, Magnesium sulphate, Pre-emptive analgesia

Introduction
Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incision and inflammatory injuries occurring during surgery and in the early postoperative period [2]. One of the major advantages of laparoscopic cholecystectomy over open cholecystectomy is reduced postoperative pain although it still remains the most common complaint in postoperative period after laparoscopy [3].
Postoperative pain after laparoscopic cholecystectomy can be divided into three major groups according to localization: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain) and shoulder pain [4]. Incisional pain predominates and is the most intense on the day of surgery and the following day. Interventions before the noxious stimulus causing central sensitization may attenuate or block sensitization and reduce acute pain and analgesic consumption [5].

Aim and Objectives
The aim of our study is to compare the efficacy of intra-operative intravenous Magnesium sulphate versus intravenous Paracetamol on postoperative analgesic requirement in laparoscopic cholecystectomy under general anaesthesia.

Objectives
1. To study role of intraoperative Magnesium sulphate infusion as perioperative analgesic.
2. To compare the efficacy of Magnesium sulphate infusion with infusion of Paracetamol in the quality and duration of postoperative analgesia in patients undergoing laparoscopic cholecystectomy under GA.
3. To study the side effects of both infusion during intra and postoperative periods.

Material and methods
After approval by the research ethics committee and written informed valid consent of the patients the proposed study was carried out in eighty ASA I and ASA II patients, aged between 18 and 60 years of either sex, undergoing laparoscopic cholecystectomy surgery at Indira Gandhi Medical College, Shimla. The study was conducted in a controlled prospective randomized manner divided in 40 patients in each group.
All patients posted for surgery were counseled about the mechanism of the drugs and their adverse effects. The procedure was explained to the patient. Informed consent was obtained. Detailed history of the patient was collected. Complete routine investigations were done. Patients fulfilling the inclusion criteria and who gave consent were then randomly allocated to one of the study groups.

Inclusion Criteria
- ASA grade I & II patients
- Laparoscopic cholecystectomy under GA
- Age 18-60yrs

Exclusion Criteria
- ASA grade III and IV patients
- Emergency surgeries

- Patient with known allergic to opioids

Patient Group: The patients were randomly divided into two groups of 40 patients each
Group1: **Paracetamol group**
Group2: **Magnesium sulphate group**
Monitoring used: NIBP, Pulse oximeter, $EtCO_2$, ECG.
Drug dosage used: Paracetamol 15mg/kg iv over 10 min as infusion and Magnesium sulphate50mg/kg iv in 100ml NS over 10 min as infusion.
All the patients are allocated into 2 groups randomly. The patients in group 1 received Paracetamol iv 15mg/kg over 10 min and patients in group 2 received Magnesium sulphate 20 mg/kg in 100ml NS over 10 min immediately after intubation before starting of surgery.
A uniform standard technique of general anaesthesia with endotracheal intubation and controlled ventilation was given for all patients. Pre anaesthetic check-up was done for all patients and baseline investigations were ordered as per requirement. 15 min before the scheduled time IV cannulation was done after shifting the patient into the recovery area of the operation theatre.
Patient was pre-medicated with Inj. Glycopyrolate 0.2mg, Inj Ondansetron 4mg, Inj. Fentanyl 1mcg/kg, Inj. Midazolam 0.02mg/kg given intravenously slowly.
On arrival into operation theatre patient was monitored for NIBP, pulse oximetry and ECG. Baseline HR, BP and Spo2 were recorded. After pre oxygenation of 3minutes with 6liters of oxygen the patient induction was done with Inj. Propofol 2 mg/kg and endotracheal intubation was performed by using Inj suxamethonium 2mg/kg and with an appropriate size oral cuffed portex endotracheal tube after direct laryngoscopy.
After intubation anaesthesia was maintained with Oxygen 33%, Nitrous oxide 66%, muscle relaxant Inj. Atracurium 0.5mg/kg and inhalational Isoflourane in the range of 0.2-1.5%. IPPV was given using circle absorbing system connected to anaesthesia work station at a rate of 14 breaths/min and 8ml/kg tidal volume. ETCO2 maintained between 30-35 mm Hg. Intra operative IV fluids (Ringer lactate and normal saline) were given. Patients were randomly allocated to receive one of the drug among the two (Inj. Paracetamol I.V 15mg/kg over 10 min and Inj. Magnesium sulphate I.V 20mg/kg in 100ml NS over 10 min before starting surgery.
Vital data was recorded at induction, intubation and every 5 min in first 30 min then after 15 min till surgery ended during intraoperative period. The parameters recorded were heart rate, SpO_2, systolic and diastolic blood pressures were noted.
After completion of surgery the neuromuscular blockade was reversed with Inj. Neostigmine 50mcg/kg and Inj. Glycopyrrolate 1mcg/kg. Vital data was recorded during recovery period. Patients were transported to the post-operative ward after confirming an adequate level of consciousness and intact reflexes and were observed for 24 hrs in postoperative period for analgesia and hemodynamics.
Postoperative pain assessment was done by using Visual Analog scale. Post operatively, the patients in both the groups were observed for 24 hours and recording were done at: 0 hr (as soon as the patient was shifted), 1hr, 3hr, 6hr, 9hr, 12hr, 18hr and 24hrs. Time of onset of rescue analgesia is noted. Inj. diclofinac sodium i.m is given if VAS >5.The results were noted, master chart prepared and statistically evaluated.

Statistical analysis
Data collected, tabulated, coded and analyzed (student-test). Numerical variables were presented as mean and standard deviations (SD). A difference with P value <0.05 was considered statistically significant. Microsoft word and excel have been used to generate tables.

Observation and results
The present study was conducted in Department of Anaesthesia and critical care IGMC, Shimla. After taking ethical committee approval, 80 patients belonging to ASA physical status I and II were randomly divided into 2 groups, 40 each based on computer generated randomization table.
Group 1: Paracetamol 15mg/kg iv over 10 min as infusion.
Group 2: Magnesium sulphate 20 mg/kg iv in 100ml NS over 10 min as infusion.

There were no clinical or statistically significant differences in the demographic profile of patients in either group. The patients' age ranged from 18-60 years. The average age did not differ between the two groups. The mean age of Group-2 was 33±11 years and that of group-1 was 40±1.The difference was not statistically significant.
In our study Group 2 contains 52.5% of females and 47.5% of males. Group 1 contains 70.0% of females and 30.0% of males. These ratios are found to be statistically insignificant.

Comparison of mean Heart Rate (per minute) in two groups
Heart rate of all patients was continuously monitored and readings were noted at regular intervals of every 5 minutes for 30 minutes and then every 15 min till surgery ended. In this study it was observed that heart rate variation is not statistically significant. ($p > 0.05$).

Table 1: Comparison of mean SBP in both groups at different time intervals Intra operatively.

Time(min)	1		2		p-Value	Significance
	Mean SBP	SD	Mean SBP	SD		
0	138	8	142	11	0.067	NS
5	132	11	128	15	0.177	NS
10	124	16	120	13	0.223	NS
15	125	15	119	18	0.109	NS
20	122	16	117	15	0.153	NS
25	119	13	115	11	0.141	NS
30	120	9	118	12	0.401	NS
45	118	10	116	12	0.420	NS
60	118	9	115	15	0.281	NS

In both group systolic blood pressure was not significant statistically at any time ($p > 0.05$).

Table 2: Comparison of mean DBP in two groups at different time intervals Intra operatively

Time	1		2		p-Value	Significance
	Mean DBP	SD	Mean DBP	SD		
0	82	8	78	11	0.066	NS
5	81	9	77	14	0.132	NS
10	79	12	77	11	0.439	NS
15	75	8	78	12	0.192	NS
20	76	8	76	10	0.100	NS
25	75	9	77	8	0.296	NS
30	74	7	76	11	0.335	NS
45	72	6	74	10	0.281	NS
60	74	7	75	11	0.629	NS

NS-not significant

In both group diastolic blood pressure was not significant statistically ($p > 0.05$) at any time.

Systolic and diastolic blood pressures were recorded in all patients at regular intervals. The results were tabulated (table no.1,2) and were subjected to statistical analysis. It was found that there was no statistically difference in variation.

We also compared the End tidal carbon dioxide pressures in two groups and found that the results ranged between 35-37Hg and were subjected to statistical analysis. It was found to be insignificant statistically ($p > 0.05$).

Table 3: Comparison of mean VAS in both groups post-operatively

Time(hr)	1			2			p-Value	Significance
	median	Mean VAS	SD	Median	Mean VAS	SD		
0	2	2	1	4	4	1	.0001	HS
1	3	3	1	4	4	2	.0059	HS
3	4	5	1	3	4	2	.0059	HS
6	3	3	1	5	5	2	.0001	HS
9	4	3	2	6	6	2	.0001	HS
12	5	4	2	5	6	1	.0001	HS
18	3	2	2	4	4	2	.0001	HS
24	2	2	1	4	4	1	.0001	HS

The value of group 2 (Magnesium sulphate infusion) is statistically significant than the patients in group 1 (Paracetamol infusion). This denotes that analgesic efficacy of Magnesium sulphate infusion is less than that of Paracetamol infusion. ($p < 0.05$)

Table 4: Comparison of time of onset of rescue analgesia in both groups

Group	Mean time of onset of rescue analgesia(hrs)	SD	p- value
1	5.8	2.37	0.0001
2	2.0	1.74	Highly significant

Patients in group I had a mean time of onset of rescue analgesia at 5.8±2.37 hours, whereas patients included in group 2 had mean time of onset of rescue analgesia as 2.0±1.74 hours. These results were tabulated and were subjected to statistical analysis. The p- value came out to be (p - 0.0001) which is highly significant.

Discussion

There is evidence that preoperative pain and inflammation cause worse postoperative pain level, probably through sensitization of the central nervous system. Although in laparoscopic cholecystectomy less postoperative pain felt but still remains the main problem. The nature and mechanisms of pain after laparoscopic cholecystectomy are multifactorial because pain originates from three sources: port wounds, pneumoperitoneum (type of gas, pressure, temperature and volume of residual gas) and cholecystectomy (visceral pain) [6]. In some studies, incisional pain predominated over visceral and shoulder tip pain3. Pneumoperitoneum causes neuropathic pain by chemical irritation, ischemia and compression [7]. Multimodal analgesic approach is recommended for the treatment of postoperative pain after laparoscopic cholecystectomy because of enhanced recovery and reduced risk of side effects [8].

NMDA receptor is an amino acid receptor in the brain and spinal cord responsible for excitatory synaptic transmission [9]. Magnesium as a NMDA receptor antagonist can prevent the induction of central sensitization after peripheral nociceptive stimulation [5].

I.V Paracetamol is a centrally acting antipyretic and analgesic has less gastrointestinal and platelet inhibiting side effects and is clinically better tolerated. IV Paracetamol could potentially provide adequate perioperative analgesia as a single agent for mild to moderate pain [10]. Diclofenac is a NSAID that mediate anti-inflammatory, analgesic and platelet inhibiting effects. This used as rescue analgesia in our study.

After taking ethical committee approval, 80 patients belonging to ASA physical status I and II were randomly divided into 2 groups, 40 each based on computer generated randomization table. In our study we compared the efficacy of intraoperative I.V. Magnesium sulphate versus I.V. Paracetamol on postoperative analgesic requirement in laparoscopic cholecystectomy under general anaesthesia Patients were divided into two groups with 40 patients in

each group. Group 1 patients received iv Paracetamol 15mg/kg. Group 2 patients received iv MgSO4 20mg/kg. The present study was conducted in Department of Anaesthesia and critical care IGMC, Shimla.

There were no clinical or statistically significant differences in the demographic profile of patients in either group. Heart rates of all patients were continuously monitored and readings were noted at regular intervals intraoperatively and post operatively for any change. In this study it was observed that heart rate variation is not clinically and statistically significant. No arrhythmias were observed on ECG in any patient of two groups. Similar results were shown in study done by T.O. seyhan et al and Shashi kiran et al.[11,12]In present study there is no change in heart rate intraoperatively and post operatively.

Similarly systolic and diastolic blood pressures and were recorded in all patients at regular intervals of 5 minutes upto 30minutes and after that every 15 min till surgery ended. The results were tabulated (table no: 1, 2) and were subjected to statistical analysis. It was found that there was no clinically and statistically difference found. Similar results were noted in study done by T.O. seyhan et al and Shashi kiran et al. [11, 12]

End tidal carbondioxide pressures were measured in all patients after creating pneumoperitoneum at regular intervals of 10 minutes till surgery ended. The results ranged between 35-37 mm Hg and were subjected to statistical analysis. It was found to be insignificant clinically and statistically.

Visual analog scale (VAS)

Each patient was explained before surgery about expression of pain by using visual Analog score. VAS was recorded after extubation 0, 1, 3, 6, 9, 12, 18 and after 24hrs. A VAS scale was used to get the severity of pain numerically from the patients. All the results were tabulated and subjected to statistical analysis. The value of group 2 (Magnesium sulphate infusion) was clinically and statistically significant than the patients in group 1 (Paracetamol infusion). This denotes that analgesic efficacy of Magnesium sulphate infusion is less than that of Paracetamol infusion.

Rescue analgesia

In present study all patients were observed for first demand rescue analgesia dose in 24 hours post operatively. When the VAS score > 5, rescue analgesia of IV Inj. Diclofenac sodium 75mg was given. Patients in group 1 had a mean time of onset of rescue analgesia at 5.8±2.37 hours, whereas patients included in group 2 had mean time of onset of rescue analgesia as 2.0±1.74 hours. These results were tabulated and were subjected to statistical analysis. The p-value came out to be (p - 0.0001) which is highly significant. This denotes duration of post-operative analgesia with Paracetamol is significantly longer than that of Magnesium sulphate infusion.

Although very fewer studies were done to compare analgesic effect of paracetamol and magnesium sulfate in past. T. O. Seyhan et al studied the analgesic effect magnesium sulfate and changes on heamodynamics [11]. In Christopher Lysakowski, MD et al randomized trials have reached different conclusions that Magnesium is a useful adjuvant to postoperative analgesia [13]. But in present study the post-operative analgesia in I.V Magnesium sulphate was short lived and average duration was 2.0±1.74 hours when rescue analgesia was administered.

Zeinab Ahmed Elseify et al and Bright Jebaraj et al concluded that intravenous Paracetamol provided better analgesia and higher patient satisfaction than each drug when used separately [14, 15]. Gousheh SM et al also concluded that Paracetamol (1gm) had caused a better pain relief quality but it is not a suitable analgesic for moderate pain control in acute phase after surgery alone [16].

This study concluded that postoperative intravenous Paracetamol is a safe and effective component of multimodal analgesic regimen, and it reduces postoperative opioid consumption after orthopedic surgery, but at present there is insufficient data to decide whether Paracetamol reduces opioid-related adverse effects or not.

In present study it has been found I.V Paracetamol administration before onset of surgery resulted in long duration of post-operative analgesia requiring rescue analgesia 5.8±2.37 post operatively. When compared to 2.0±1.74 in Magnesium sulphate group. The values are statistically significant. There are no significant changes heart rate, blood pressure and $ETCO_2$ in both the groups. No other significant side effects were found in any of the groups.

Conclusion

1. I.V Paracetamol infusion is observed to be superior analgesic drug for perioperative analgesia than Magnesium sulphate infusion.
2. Both groups do not have any changes in haemodynamics and $EtCO_2$ of the patients.

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