A prospective, randomized, double blind study to evaluate Morphine sparing effect of IV paracetamol in laparoscopic cholecystectomy.

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Abstract:
Objective: The study evaluated the analgesic efficacy and morphine sparing effect of intravenous Paracetamol afterlaparoscopic cholecystectomy.
Method: Eighty patients wererandomized into two groups to receive either 100 ml (1000mg) Paracetamol (group I) or 100 ml normal saline (group II) 30 minutes before induction with 50% or full dose of morphine at induction .In the recovery room pain intensity was evaluated and the time of first request for analgesic and morphine consumption was noted. Side effects of morphine if any, were recorded.
Results: Mean time of rescue analgesia from induction in the study group was 12.8±3.4hrs and in control group was 7.0±4.8 hrs. (P = 0.000) The mean number of administered doses of rescue analgesia during 24hrs in the study group was 0.5 ± 0.5 and in the control group it was 1.3 ± 0.4. (p = 0.000) with significant difference in morphine consumption,12.2 ± 2.1 vs7.1± 1.6 respectively in the immediate postoperative period. The episodes of nausea and vomiting in the study group were 0.7 ± 0.7 in comparison to 1.1 ± 0.8 in the control group during 24hrs of surgery.(p = 0.056)
Conclusion: Administration of IVparacetamol and 50% dose of morphine in patients undergoing laparoscopic cholecystectomy ensures effective analgesia intraoperatively as well as postoperatively when compared with full dose of IV morphine without affecting morphine-related adverse effects in these patients.
Keywords: Paracetamol; Morphine; Laparoscopy; cholecystectomy;

I.   Introduction

Acute pain after laparoscopic cholecystectomy is complex in nature and does not resemble pain after other laparoscopic procedures.[1] General anaesthesia with intravenous opioid analgesic using morphine or fentanyl is a standard procedure.[2] However, the use of these medications is associated with side effects such as nausea, vomiting, sedation, and delayed recovery. Prescribed method for minimizing opioid related side effects is concomitant administration of a nonopioid analgesic.[3] Intravenous paracetamol has recently been used intraoperatively to decrease requirement of opioids for postoperative analgesia and has been found to have comparable efficacy to pethidine for postoperative pain in tonsillectomy in children.[4]

While Paracetamol has been used for pain control after surgery[5]the use of this drug prior to induction of anesthesia for the postoperative pain control is the main aim of this research that determined its analgesic efficacy, opioid sparing effect and attenuation ofopioid related side effects after laparoscopic cholecystectomy.

II.   Material And Methods

This prospective randomized study was conducted in Department of Anaesthesiology and Critical care atSher-i-Kashmir Institute of Medical Sciences Soura Srinagar Kashmir. Eightyfemale patients of physical status ASA I and II   in the age group of 18-50 years scheduled for laparoscopic Cholecystectomy were selected for the study. Patients with history of allergic reactions to paracetamol or morphine, hepatic failure, pregnancy, ASA> II were not included in the study. Preoperatively use of Visual Analogue Score (VAS) scale was demonstrated to the patients consenting for the study. No premedication was given to any patient.

On arrival to operation Theatre intravenous line was secured. Electrocardiography (ECG), Noninvasive blood pressure (NIBP), Pulse oximetry (SpO_2) was monitored prior to induction and intraoperatively till the extubation was achieved.

We recruited 80 patients and as per randomization these patients were allocated to one of the groups (n = 40) to receive following drug mixtures.

Group I (Study group): Received intravenous 100ml(Paracetamol 10mg/ml) 30min prior to induction in anaesthetic room and 50 µgm/kg morphine diluted with normal saline to a total volume of 10ml at induction.

Group II (Control group): Received 100 ml normal saline 30 minute prior to induction and100 µgm/kg morphine in 10ml normal saline at induction.

Each patient was induced with Propofol; muscle relaxation achieved with 0.5mg/kg Atracurium for endotracheal intubation . The anesthesiologist involved in anaesthetizing the patients was blinded to the analgesic regimen. Upto 50µgm/kg of morphine could be used as rescue analgesic intraoperatively depending on the decision of the anesthesiologist.Anesthesia was maintained with equal mixtures of O_2 and N_2O in 0.6 - 1.5%isoflurane. Controlled ventilation was used to achieve $ETCO_2$of 30-35mmHg. Vital signs were recorded every 5 minutes during the procedure. Granisetron 40µgm/kg was injected 15min prior to reversal of anesthesia. At the end of surgery, neuromuscular block was reversed and patient extubated awake.

In the Post anaesthesia care unit (PACU), vital signs were recorded every 10 minutes for 1st 30 min. Pain if any was assessed by VAS. If VAS was >3 on a scale of 0 - 10, rescue analgesia was given as 3 mg bolus of morphine intravenously. Pain was assessed after 10 min and repeat dose of morphine was given if VAS was still >3. Side effects such as nausea and vomiting were recorded in first 24 hours period. Inj. prochlorperazine 12.5mg intravenous was given as rescue anti emetic and repeated 8hourly if necessary.

If patients did not need rescue analgesia in PACU but needed it in the postoperative period in the surgical ward, Injection ketorolac or Tramadol was administered as rescue analgesia by the surgical staff and the time when rescue analgesia administered was noted as the time to first request of analgesia.

Statistical analysis.Metric data was compared by student's t-test and non-metric by chi-square test at 95% CI (confidence interval) respectively. Metric and non-metric data was expressed as mean ± standard deviation (SD) and percentages. Metric data was compared by student's t-test and non-metric by chi-square test at 95% CI (confidence interval) respectively. SPSS 11.5 MS excel andMinital-software were used for data analysis.

III.   Results

The data analysis showed both groups were comparable regarding theirage, ASA status, BMI and duration of surgery. (Table I).

Table I. Demographic data**.**

Demographics	Study group (I)	Control group (II)	P value
Age (yrs.)	35.4 ± 9.2	38.8 ± 8.1	0.089 (NS)
ASA class I/II	40/0	37/3	0.077(NS)
BMI (kg/m^2)	25.3 ± 3.32	26.2 ± 2.73	0.621 (NS)
Duration of surgery (min)	41.5±8.1	40.6±9.9	0.667 (NS)

Data presented as mean ± standard deviation

Comparison of Mean heart rate, systolicblood pressure, and diastolic blood pressure between the two groups measured at 5-minute intervals between the two groups was insignifiant. (p> 0.05). The median value of pain scores was found significantly lower atall time intervalsin-group I when compared to group II (Table II). Mean time of rescue analgesia from induction i.e. duration of analgesia was 12.8±3.4hrs and 7.0±4.8 hrs in study and control group respectively(P = 0.000).(Figure I)None of our patients in either group required an additional dose of morphine intraoperatively.

Table II. Pain scores at different intervals between the two groups.

Visual Analogue Score (VAS)			
Time	Study group (I)	Control group (II)	p value
0 hr.	0.4 ± 0.6 (0, 3)	2.2 ± 0.8 (1, 4)	0.000 (Sig)
4 hrs	1.9 ± 0.8 (1, 5)	3.2 ± 0.9 (2, 5)	0.000 (Sig)
8 hrs	2.4 ± 0.5 (1, 3)	3.2 ± 0.7 (2, 5)	0.00 (Sig)
12 hrs	2.8 ± 1.2 (1, 5)	3.4 ± 0.9 (2, 5)	0.026 (Sig)
16 hrs	1.9 ± 1.0 (1, 4)	2.4 ± 1.0 (1, 5)	0.037 (Sig)
20 hrs	1.3 ± 0.8 (0, 3)	1.7 ± 0.8 (0, 3)	0.030 (Sig)
24 hrs	0.7 ± 0.8 (0, 2)	1.1 ± 0.8 (0, 2)	0.030 (Sig)

Data presented in mean ± standard deviation

The total consumption of morphine as rescue analgesic in PACU was significantly higher in control Group.The total numberof rescue analgesia doses injected over 24 hours showed a significant difference between the two groups with p value of 0.000 (Table III).

TableIII. Post operative analgesia requirement, pain relief and side effects.

Variable (Mean ± SD)	Study group (I)	Control group (II)	P value
Morphine consumption (Intraoperative)	0	0	NA
Morphine consumption (PACU)	7.1± 1.6	12.2 ± 2.1	0.01 (S)
Duration of analgesia (hrs)	12.8 ± 3.4	7.0±4.8	0.000 (S)
Mean Aldrete Score	9.7 ± 0.5	8.0 ± 1.2	0.000 (S)
Mean stay in PACU (min)	25.12 ± 14.52	41.12 ± 14.99	0.022 (S)
Incidence of sedation	1.2 ± 0.12	2.3 ± 0.01	0.063 (NS)
Episodes of PONV	0.7 ± 0.7	1.1 ± 0.8	0.056 (NS)
No. of rescue doses in 24 hours	0.5 ± 0.5	1.3 ± 0.4	0.000 (S)

Data presented in mean ± standard deviation

Mean Aldrete Score in the study group was 9.7 ± 0.5 and in the control group it was 8.0 ± 1.2 and was found to be statistically significant with a P value of <0.05. The episodes of nausea and vomiting in the two groups did not show any statistical significance. (p = 0.056). None of the patients experienced symptoms of respiratory depression during postoperative period. No late complications were reported

IV. Discussion

Recent advancements in surgical techniques have resulted in shorter, less invasive procedures, and newer anaesthetic agents have facilitated rapid recovery with fewer side effects. These improvements have resulted in a tremendous increase in scope and extent of surgical procedures performed on an ambulatory basis.

Post operative pain, nausea and vomiting could delay the discharge of patients and even could result in overnight admission in the inpatient department. Use of intravenous opioids is the mainstay of pharmacological therapy for intraoperative and immediate postoperative analgesia and these are known to produce postoperative sedation and increased nausea and vomiting.

In a prospective study in laparoscopic cholecystectomy, Fleisher et al in 1999 reported that all the patients met discharge criteria within 6 hours of surgery. 94% of patients required only oral analgesics, 12% of patients experienced postoperative nausea and vomiting requiring parenteral therapy and 3% required an additional day in the hospital.[6] .

This is the first prospective, randomized, controlleddouble blind study to look at the role of intravenous paracetamol injected 30 minutes before induction of anaesthesia in reducing intraoperative and postoperative

morphine requirements in patients undergoing laparoscopic cholecystectomy, so that optimum analgesia is achieved with a concomitant reduction in opioid related side effects.

The overall pain after laparoscopic cholecystectomy is a conglomerate of three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (referred from visceral pain). Besides showing individual variation in intensity and duration, the pain is often unpredictable. It may even remain severe throughout the first week in 18% of the patients.[7]The complex nature of pain after laparoscopic cholecystectomy suggests that effective analgesic treatment should be multimodal.[8]

In our study, we used intravenous paracetamol 1 gm. as pre-emptive analgesic in laparoscopic cholecystectomy and assessed its effects on intraoperative analgesic requirement, post-operative analgesic effectiveness, post-operative morphine consumption and frequency of side effects. Our study showed that intravenousparacetamol when used as pre-emptive analgesic just before induction as part of multimodal analgesic regime has significant opioid sparing effect. This is consistent with the findings in various studies where opioid-sparing effects of NSAIDs, COX-2 inhibitors, and paracetamol have been found to be in the range of 20–30%.[9,10] Thereis evidence from other surgical procedures to support clinically relevant analgesic effect of paracetamol with additives (Opioids, NSAIDs etc.) in laparoscopic cholecystectomy.[11,12] It has been reported in previous studies that proparacetamol behaves favorably with different ketorolac doses producing a 31–37% decrease in the morphine requirement during the first 24 h after surgery.[13]Olonisakin et al demonstrated improved analgesia and reduced morphine consumption in the immediate postoperative period with reduced opioid side effects and better patient satisfaction with IVparacetamol in patients undergoing lower abdominal gynecological surgery.[14]Our study results are consistent with all previous findings in this regard.

Our study demonstrated the additive effect of combining intravenous paracetamolwith morphine on postoperative analgesia resulting in decreased opioid amount, improved and longer duration of pain relief.(Figure I) The median pain scores were significantlylower in the paracetamol group at all intervals in 24-hourperiod.The different sites of action of these drugs in the nervous system may be the cause of better pain relief. Whereas the effect of Paracetamol is due to the inhibition of prostaglandins and activation of descending serotonergic inhibitory pathways,[15,16]the analgesic effect of morphine is due to its agonist action on opioid receptors of the central nervous system. Piguetet al.[17] had demonstrated the close correlation between plasma concentration and analgesic effect of paracetamolwith intravenous doses of up to 2 gm. in healthy volunteers.

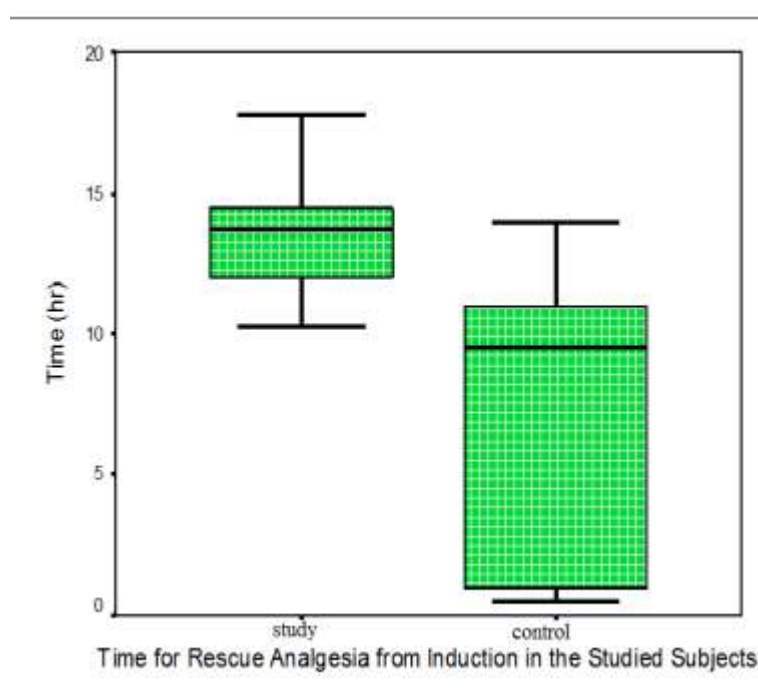Figure I.Comparison of duration of analgesia between the two groups.

Our study did not find any reduction in the opioid related side-effects (PONV, sedation etc.) in the paracetamol group (Group I) as might be expected because of the decrease in total morphine dose..At present there is insufficient data to decide whether paracetamol reduces opioid-related adverse effects or not.McNicolet al[18] performed a systematic search for single-dose, randomized, controlled clinical trials of propacetamol or intravenous paracetamol for acute postoperative pain in adults or children. Patients receiving propacetamol or intravenousparacetamol required 30% less opioid over 4hr and 16% less opioid over 6hr than those receiving placebo. However, this did not translate to a reduction in opioid-induced adverse events. Another systematic review in 2010 found that paracetamol along with PCA after major surgery reduces mean morphine consumption by6.34 mg (95% CI 3.65–9.02) in 24 hrs. But they also did not find any difference in postoperative nausea and vomiting.However, use of NSAIDS and COX-2 inhibitor causes a decrease in morphine consumption and decrease in PONV also.[19]

We concluded that administration of intravenousparacetamol and 50% dose of morphine prior to induction in patients undergoing laparoscopic cholecystectomy ensures effective analgesia intraoperatively as well as postoperatively and was associated with earlier readiness for discharge from PACU when compared with full dose of intravenous morphine. However above combination was not able to decrease the occurrence of morphine-related adverse effects in these patients.

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