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Original Article

Comparison of IV Paracetamol with IV Opioid Analgesics in Management of Post-Operative Analgesia in Laparoscopic Cholecystectomy

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ABSTRACT

Objective: To compare the efficacy of intravenous Paracetamol versus intravenous Tramadol in terms of post-operative analgesia in patients undergoing laparoscopic cholecystectomy.
Study Design: Quasi-experimental study.
Place and Duration of Study: Department of General Surgery, Pak-Emirates Military Hospital (PEMH), Rawalpindi Pakistan, Jan 2020 to Feb 2021.
Methodology: A total of 88 patients admitted for planned laparoscopic cholecystectomy were screened as per the selection criteria and were included in the study. They were further divided into two Groups. Each Group received 44 patients. Group-A received intravenous Paracetamol 1 g, while Group-B received intravenous Tramadol 100 mg, both given 6 hourly over 24 hours. Both Groups were evaluated for pain at regular interval via a Visual Analog Scale for pain, for the first 24 hours post-operatively.
Results: Mean Visual Analog Scale score post-recovery at 0 minutes was 6.57±1.47 with Paracetamol and 6.84±1.39 with Tramadol, (p=0.38). The difference in both Groups remained non-significant when checked at regular intervals till 18 hours post-recovery where intravenous Paracetamol showed a clearly superior Visual Analog Scale score of 1.00±0.94 versus 1.66±1.06 with Tramadol, (p= 0.007). Thereafter, the difference disappeared again at 24 hours post-recovery.
Conclusion: Paracetamol provides analgesia effectively when compared to Tramadol in the first 24-hour post-operative period. Moreover, it seems to be devoid of the adverse effect profile seen with opioid analgesics. Considering the results obtained, the routine use of Paracetamol as first-line analgesic post-operatively is highly recommended.

Keywords: Laparoscopic cholecystectomy, Paracetamol, Post-operative analgesia, Tramadol

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INTRODUCTION

Laparoscopic cholecystectomy is one of the most commonly performed laparoscopic procedures in general surgery today, due in part to it being regarded as a routine procedure requiring a shorter hospital stay.[1] Post-operative pain is one of the most common complaints encountered, however, a multitude of different pre-, peri- and post-operative regimens are currently in practice worldwide to overcome this complication in order to facilitate an early discharge from hospital and a return to normal life, which is one of the primary advantages of laparoscopic procedures.[2,3]

The mechanism for development of pain after laparoscopic procedures differs slightly from those in open procedures where the pain is parietal in origin, in contrast to laparoscopic surgery, which has an added, and more predominant visceral pain component due to the production of artificial pneumoperitoneum and remnant carbon dioxide in the sub-diaphragmatic space, which often persists post-surgery and causes local irritation.[4] Symptomatic cholelithiasis is an exceedingly common presentation of the female surgical abdomen and it is common hospital policy to use minimally invasive laparoscopic cholecystectomy for such patients. Multiple different pain control regimens have been described ranging from local anesthetic infiltration in port sites, and/or intra-peritoneal infiltration to pre-, peri- and post-operative regimens based on oral drug Groups like gabapentinoids, non-steroidal anti-inflammatory drugs (NSAIDs), Paracetamol, intravenous glucocorticoids and opioids, or more novel techniques such as port size reduction (3mm) and transversus abdominis plane block. Both opioids and NSAIDs are considered as important tools in the repertoire of the general surgeon and anesthetist against pain.[5,6] Paracetamol has good analgesic and antipyretic properties with minimal systemic effects, resulting in its support in a large number of studies. Its use as an analgesic has been advocated in various studies and has shown to be effective in relieving post-operative pain following laparoscopic cholecystectomy.[7,8] Tramadol, a synthetic opioid which belongs to amino cyclohexanol Group, delivers its analgesic effects by acting centrally and has weak opioid agonist properties. It is also considered to have a role in providing analgesia in post laparoscopic cholecystectomy, with a good

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safety profile.[9,10]

Inadequate analgesia in the post-operative phase is an unwarranted complication of elective surgery, which, not only, puts the surgeon's reputation and the institution's practices under a dark cloud, may also result in unnecessary over-prescription of opioid analgesics. As a result, this study was conducted to find an economical and more efficacious alternative to opioid analgesics in the early post-operative phase to achieve the optimum outcome in terms of morbidity, and financial costs, especially with regards to shortened hospital stay, and an early, smooth recovery.

METHODOLOGY

The quasi-experimental study was conducted from January 2020 to February 2021 at the Department of General Surgery, Pak-Emirates Military Hospital, Rawalpindi, Pakistan, after gaining approval from the Institutional Ethics Review Committee. The sample size was calculated using the WHO sample size calculator keeping the population standard deviation (σ) and variance (σ2) of 0.67 and 0.4489, respectively, and test value of the population mean and anticipated population mean of 3.53 and 4.2, respectively.[11] Sampling was done via a computerized lottery method.

Inclusion Criteria: Adult patients of either gender, between 18-65 years of age, with symptomatic cholelithiasis, American Society of Anesthesiologists (ASA) I or ASA II, who were scheduled for elective laparoscopic cholecystectomy under general anesthesia and who were ready to stay in hospital for 24 hours after surgery, were included.

Exclusion Criteria: Pregnant and lactating patients, those with known allergy to Tramadol or Paracetamol, patients on chronic analgesic medications, patients with significant coronary artery disease or ischemic myocardial disease, drug or alcohol abuse, chronic pulmonary disease, renal failure, hepatic dysfunction, and hemorrhagic disorders were excluded from the study. Those who had acute cholecystitis at the time of surgery or had prolonged surgery due to difficult cholecystectomy were also excluded.

A total of 88 patients were enrolled after obtaining informed consent. All patients were kept nil by mouth from midnight before surgery and given Ketorolac 30 mg in 100 mL normal saline just before surgery. A standard 4-port laparoscopic cholecystectomy was performed, with a 10 mm trocar placed using the open technique through an infra-umbilical incision, while the remaining ports were inserted under direct vision. Following dissection and ligation of the appropriate vessels and ducts, the gall bladder was extracted from the 10 mm port placed in the epigastric region. Intra-peritoneal local anesthetic was injected at the liver bed before port removal. This was followed by release of the pneumoperitoneum, after which intra-incisional local anesthetic was injected at all four port sites. Non-absorbable, mono-filament sutures were then used to close the port sites. Patients were shifted to recovery area and randomly divided into two Groups by lottery method (Figure). The patients in Group-A received intravenous Paracetamol at a concentration of 1 g in 100 mL normal saline solution, while Group-B received intravenous Tramadol at a concentration of 100 mg in 100 mL normal saline. The first dose was given to patients on arrival in recovery area and thereafter repeated at 6, 12 and 18 hours after the first dose. Pain intensity was measured on a 10-point Visual Analogue Scale (VAS, where 0 equaled to no pain and 10 stood for the worst pain imaginable). VAS scores were obtained postoperatively at the following points: just before analgesic administration (T0), 0.5 hours (T1), 1.5 hours (T2), 3 hours (T3), 6 hours (T4), 12 hours (T5), 18 hours (T6) and 24 hours (T7) after the first dose. Any pain score above 5 on VAS was considered breakthrough pain and was managed with rescue analgesia using intravenous Ketorolac 30 mg in 100 mL normal saline, as needed.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables with normal distribution were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics.

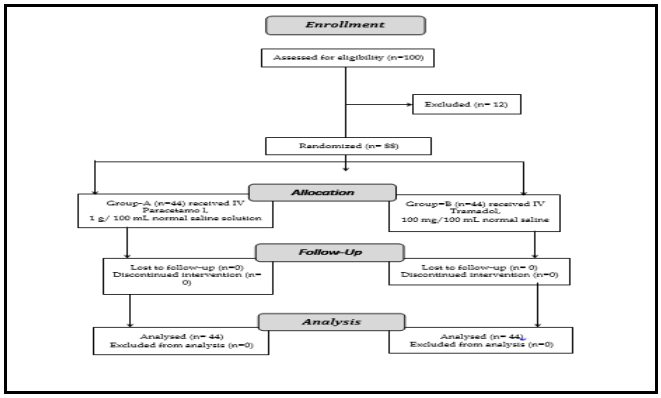

Figure: Patient Flow Diagram (n= 88)

RESULTS

A total of 88 patients were studied, 27(30.7 %) of whom were male and 61(69.3%) were female. The mean age of the sample was 53.23±8.49 years. 24(27.3 %) patients were found to be ASA I, while 64(72.7%) were seen to fall in ASA II category. The patient and surgery characteristics are shown in Table- I. None of the variables showed any significance across both Groups.

Results for post-surgery VAS pain evaluation for the first 24 hours are shown in Table-II. The VAS scores were measured just before analgesic administration (T0), and then 0.5 hours (T1), 1.5 hours (T2), 3 hours (T3), 6 hours (T4), 12 hours (T5), 18 hours (T6) and 24 hours (T7) after the first dose.

VAS scores at 18 hours were significantly lower in Group A, when compared to Group B, (p=0.003). With regards to the other time periods where pain was measured, it was seen that there was no statistical difference between the two Groups in terms of pain scores. A total of 18(20.5 %) patients developed breakthrough pain while 70(79.5 %) patients did not, the difference between the two Groups was not statistically significant (p=0.29). Only 1(2.2 %) patient in Group B complained of nausea and was managed with injection ondansetron 4 mg intravenous infusion.

Table-I: Patient and Clinical Characteristics (n=88)

Variables	Group-A	Group-B	*p*-value
Gender			
Male Patient	15(17.1 %)	12(13.6 %)	0.48
Female Patient	29(32.9 %)	32(36.4 %)	
Age (years)	53.30±8.50	53.16±8.58	0.94
Body Mass Index	29.68±3.55	29.08±3.41	0.42
ASA Class			
ASA I	11(12.5 %)	13(14.8 %)	0.63
ASA II	33(37.5 %)	31(35.2 %)	
Total Operation Time (mins)	52.70±13.62	50.79±9.15	0.44

Table-II: Pain Scores in the Study Groups (n=88)

Variables	Group-A	Group-B	*p*-value
VAS Score T0	6.57±1.47	6.84±1.39	0.38
VAS Score T1	2.98±1.98	3.11±1.47	0.72
VAS Score T2	2.77±1.27	2.29±1.17	0.07
VAS Score T3	1.61±1.22	1.81±1.16	0.43
VAS Score T4	1.66±1.16	1.89±1.28	0.39
VAS Score T5	1.57±1.04	1.73±0.97	0.46
VAS Score T6	1.00±0.94	1.66±1.06	0.003
VAS Score T7	0.91±0.68	1.05±0.68	0.35
Breakthrough Pain			
Present	11(12.5 %)	7(8.0 %)	0.29
Absent	33(37.5 %)	37(42.0 %)	

DISCUSSION

Pain is one of the most significant concerns for patients undergoing surgery. Daycare surgeries like laparoscopic cholecystectomy require effective pain management in order to attain the full utility of this minimally invasive procedure and facilitate early recovery. Intravenous Paracetamol is an effective analgesic with a good safety profile via inhibition of COX-3 receptors and at the spinal cord level. In addition, it acts on NMDA, substance P, and nitric oxide pathways.[12]

The majority of the patients in our study were female 61(69.3%) similar to Upadya *et al* who conducted a similar study where, while still in majority, females accounted for 58.3% of the sample (n=35).[13] Arslan *et al* reported on a study population with a female proportion of 66.3% (n=199).[14] In contrast, Uztüre *et al*. reported a population with men in majority, accounting for 56.6% (n=34) of the sample population.15 We believe that a female preponderance of patients in sample of cholecystectomy candidates is consistent with existing data as increase in male patients in some studies may be due to a selection bias.

The mean age of the patients in our study was 53.23±8.49 years. Zavareh *et al*. studied a much younger population of 38.15±9.15 years,[16] while Arslan *et al* reported on a comparatively older population of 42.93±8.06 years.[14] The difference here may be accounted for by a selection bias encountered in our study where the population was primarily drawn from active military service, which has lower incidence for risk factors for cholelithiasis, such as obesity, during service, resulting in a later presentation to hospital.

The mean VAS score immediately on recovery from anesthesia in our study was 6.57±1.47 with Paracetamol and 6.84±1.39 with Tramadol, which was not statistically significant. This was followed by a downward trend in both Groups, the differences remaining non-significant statistically until 18 hours post-recovery where Paracetamol showed a clearly superior VAS score of 1.00±0.94 versus 1.66±1.06 with Tramadol (p=0.007). Thereafter, the difference disappeared again till last check at 24 hours post-recovery. Bandey *et al*. demonstrated significant superiority of Paracetamol over Tramadol at 0.5 hours, 1.5 hours, 6 hours, and 12 hours with p values of 0.014, 0.018, <0.001 and 0.012, respectively.[11] Gousheh *et al* also demonstrated a similar benefit.17 Zavareh *et al* demonstrated that Tramadol was superior to a combination of Paracetamol/codeine at all times up to 24 hours in terms of VAS score (p <0.05 at all times measured) with a cumulative VAS score of 2.1±1.0 for Tramadol versus 3.8 ± 2.0 for Paracetamol/codeine Group, (p < 0.05).[16] We attribute this difference to the lower dose of Paracetamol used in the latter study (325 mg) compared to ours (1 g).

Upadya *et al*. compared intra-peritoneal bupivacaine to Paracetamol and found that there was no statistical difference between the VAS scores of both drugs until 24 hours.[13] Arslan *et al*. compared VAS scores for patients on intravenous Paracetamol versus placebo and found that the former significantly improved VAS score at all stage up to 24 hours.[14] Durak *et al*. demonstrated that intravenous Paracetamol was equivalent to diclofenac in ameliorating requirement for opioid analgesia for breakthrough pain,[18] a finding that was concurrent with Abdulla *et al*. and Medina-Vera

et al. when comparing Paracetamol to intravenous parecoxib and ketorolac.[19,20]

The administration of Paracetamol parenterally and orally in pre, peri and post-operative phase has proven to be effective in providing effective post-operative analgesia and reducing the requirement of additional analgesics. Evidence from our study and other similar studies show that intravenous Paracetamol is useful both alone and in combination with other drugs. Paracetamol is an inexpensive and readily available drug that has an excellent safety profile, which is severely under-utilized in surgical practice. The intensity of post-operative pain can span a wide range depending on patient tolerance as well as patient habitus, co-morbidities, and characteristics of the surgery. Paracetamol has been shown to be as effective as other conventionally used agents for post-surgical pain relief such as NSAIDs and opioids. Consequently, the use of this medication as the sole first-line agent should be encouraged. Furthermore, the drug also shows promise for use as an adjuvant to other analgesics such as opioids, a premise which requires further scientific study.

LIMITATIONS OF STUDY

Our investigation was constrained by several methodological factors, including a limited sample size, absence of a placebo-controlled arm, and lack of double-blinding procedures. These limitations may have introduced potential sources of bias and reduced the statistical power of our findings.

CONCLUSION

Both Paracetamol and Tramadol are safe and efficacious in the management of post-operative pain in post-laparoscopic cholecystectomy, however Paracetamol appears to show comparable results in terms of objective pain assessments and has a better safety profile. As such, intravenous infusions of Paracetamol for maintenance analgesia is recommended over opioid analgesics as first-line for postoperative pain relief in patients undergoing laparoscopic cholecystectomy.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MAZ & MQB: Conception, study design, drafting the manuscript, approval of the final version to be published.

MZF & MFS: Data acquisition, critical review, approval of the final version to be published.

MAZ & IFM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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