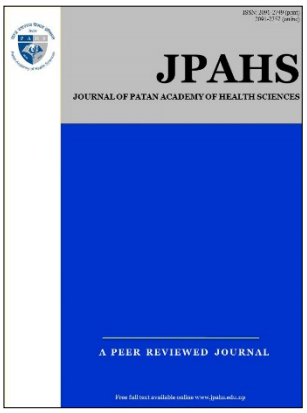

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Intravenous paracetamol vs tramadol for pain management in patients with acute pancreatitis

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Abstract

Introduction: Acute Pancreatitis causes severe and persistent pain, and thus, necessitates effective treatment. Opioids are widely used to relieve pain in acute pancreatitis due to their efficacy and effectiveness. Intravenous paracetamol has been documented to have comparable effectiveness as that of opioids, with lesser side effects. In this study, the analgesic efficacy of tramadol, an opioid was compared with paracetamol in acute pancreatitis.

Method: This was an open label comparative study conducted in a tertiary referral hospital of Nepal. Patients with Acute Pancreatitis were randomly assigned to receive 1 g of paracetamol or 50 mg of tramadol with 100 mL normal saline within 4-5 minute. Pain measurements of the patients were conducted at baseline and 24 hours after the treatment intervention. Changes in pain scores were calculated by subtracting the mean scores at baseline and 24 hours as pairs.

Result: In this study, 80 patients were enrolled and included in the final analysis. The study subjects had a mean age of 39.33 +/- 13.3 years and 62(77.5%) of them were male. Alcohol was the etiology for pancreatitis in 67.5% (n=54) of patients. Mean pain scores at baseline and 24 hours were similar in the two groups. Similarly, change of scores from baseline to 24 hours did not differ between the groups. Comparison of pain improvements failed to reveal any differences between groups.

Conclusion: Intravenous paracetamol is an effective alternative to tramadol in pain management of acute pancreatitis.

Keywords: acute pancreatitis, pain management, paracetamol, tramadol

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Introduction

Acute pancreatitis is an acute inflammatory condition of the pancreas.[1] It generally causes severe and persistent pain, and thus, necessitates effective pain management.[2]

Consensus has not yet been reached as to which analgesics are useful in treating pain in patients with acute pancreatitis.[2] Opioids are commonly used to manage such pain, although some of its clinical effectiveness and safety are still debatable.[1,2] On the other hand, intravenous paracetamol is a cyclooxygenase inhibitor that has been documented to have comparable effectiveness with opioids in an emergency setting, and in various acute pain patterns.[3,4] However, the efficacy of intravenous paracetamol, and whether it is a suitable alternative to opioids is still a subject of research. A study from Western Nepal demonstrated that IV paracetamol has better analgesic effect compared to IV diclofenac.[5]

In this study, the analgesic efficacy of tramadol, a synthetic opioid, was compared with paracetamol in adult patients with acute pancreatitis.

Method

This was an open label randomized study conducted from August 2019 to January 2020 in Gastroenterology Unit of Bir Hospital, National Academy of Medical Sciences (NAMS), Nepal. Ethical approval was obtained from the institutional review board (IRB) of NAMS. The trial was registered in the University hospital Medical Information Network (UMIN), Japan database UMIN-000037790 (https://www.umin.ac.jp/ctr/index.htm).

Patients of age 18 years or older, with diagnosis of Acute Pancreatitis, irrespective of severity were included in the study after informed consent. Acute pancreatitis was diagnosed according to the revised Atlanta Classification 2012, which requires that two or more of the following criteria be met for the diagnosis: (a) abdominal pain suggestive of pancreatitis, (b) serum amylase or lipase level greater than three times the upper normal value, or (c) characteristic imaging findings. Patients with severe hepatic impairment, severe renal impairment (CrCl<30ml/min), ongoing treatment with NSAIDs (within 24 hours), history of allergy to paracetamol, and/or tramadol were excluded from the study. Clinical, epidemiological, baseline laboratory and radiographic data-Ultrasonography (USG) Abdomen, Chest x-ray, CT Abdomen (if done) were collected by interview method by researchers.

A sealed envelope method was used for randomization to assign eligible patients to one of the two treatment groups in 1:1 ratio. All the patients received standard medical treatment including early IV hydration, nutritional support, pain control and treatment of underlying issues. For pain control, participants were intravenously administered either 1000 mg paracetamol, or 50 mg tramadol in 100 mL NS within 4-5 minutes as dictated by the study group. Patients with inadequate pain relief (visual analog scale of ≥5) at 24 hours were administered intramuscular injection pethidine 25 mg as a rescue drug. Patients were discharged once they could tolerate oral feeding and became pain free.

A 10 cm visual analog scale (VAS) displaying numbers between 0 and 10 (0 cm, no pain and 10 cm, worst pain) was used to measure pain intensity. Pain measurement of the patients was conducted at baseline (just before administering the drug) and 24 hours after the treatment intervention. Patients were blinded to previous VAS scores. Patients were also asked if they required rescue drug at the end of the study. Adverse effects, such as allergic reaction, nausea and vomiting, and others reported by participants, were also recorded. Patients with nausea and vomiting were treated with antiemetics and the study drug was discontinued in case of serious adverse effects.

The primary objective was to compare the efficacy of intravenous paracetamol with tramadol for pain management in acute pancreatitis. The secondary objective was to determine number of patients with drug-related adverse events, causes of acute pancreatitis, and impact of two drugs on duration of hospital stay. We also tried to analyze incidence of severity of acute pancreatitis as per the revised Atlanta Classification.[6]

By considering that the difference of less than 10% is of no clinical significance, and the non-inferiority margin of -0.1, the sample size was calculated by using the mean response rates of tramadol (90%) and paracetamol (80%) in the study done by Gulen B et al.[7] It was calculated that a total 78 patients (39 in ach arm) would be required for the analysis with an alpha error at 0.05 and the power of study at 80%.

We used intention-to-treat analysis for all efficacy analyses, analyzing all participants who underwent randomization. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as numbers and frequencies. Categorical variables were compared using descriptive statistics and continuous variables with independent t test. Bivariate analysis was carried out to assess efficacy of two drugs. All statistical analyses were performed using the SPSS 20.0 statistical package.

Result

A total of 80 patients were included in the study with 40 in each group, Figure 1.

The study period was of six months, from August 2019 to January 2020. The patients had a mean age of 39.33 +/- 13.3 years and 77.5% (n=62) were male. Furthermore, in majority (67.5%, n=54) of the patients alcohol was the cause of pancreatitis, documented gallstones and biliary etiology for pancreatitis was seen in 11.25% (n=9) of the patients, biliary plus alcohol was seen in 2.5% (n=2), hypertriglyceridemia, post ERCP pancreatitis and Intrapapillary Mucinous Neoplasm (IPMN) were seen in 1 each, and unknown cause was seen in 15% (n=12).

Table 1. Baseline characteristics of the patients with acute pancreatitis (AP), N = 80

Mean Age +/- SD	**39.33+/-13.4**
Gender –Male n (%)	62 (77.5)
Clinical symptoms and signs n (%)	
Nausea	50 (62.5%)
Vomiting	42 (52.5%)
Abdominal Tenderness	26 (32.5%)
Guarding	5 (6.3%)
Muscle rigidity	0 (0%)
Etiology for pancreatitis n (%)	
Alcohol	54 (67.5%)
Biliary	9 (11.25%)
Others	17 (21.25%)
Severity of AP as per revised Atlanta Classification	
Acute	50 (62.5%)
Moderately severe	22 (27.5)
Severe	8 (10)

As per the revised Atlanta classification[6], 50 (62.5%) had mild acute pancreatitis, Table 1.

When compared in both the groups, the distribution of mild, moderate and severe pancreatitis was similar in both the groups.

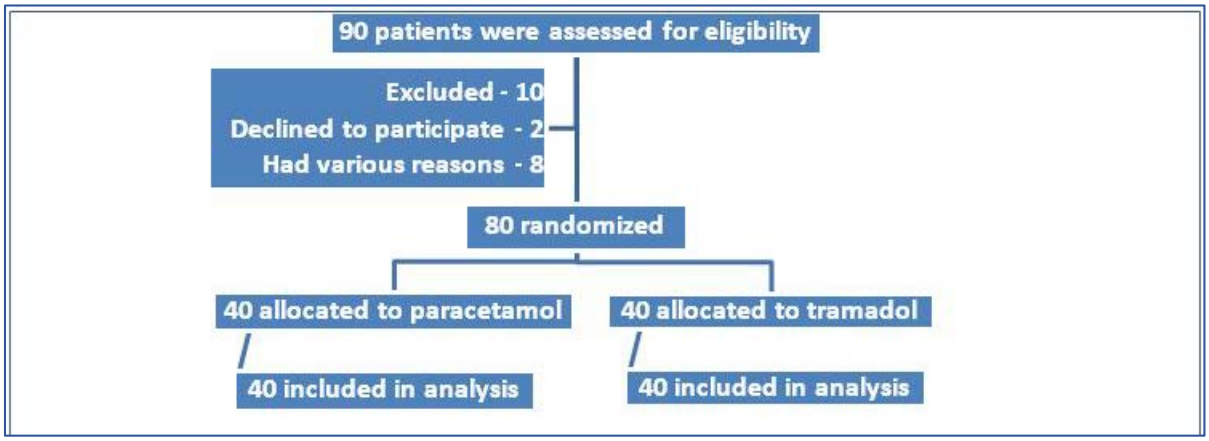

Figure 1. Flow Diagram of the participants in the study

Table 2. Change in pain intensity at baseline and 24 h for each group of patients with acute pancreatitis (AP)

Variable	Paracetamol Group	Tramadol Group	p value
Baseline VAS (mean)	7.6	7.93	
24 Hours VAS (mean)	0.98	1.43	
Change from Baseline (mean)	6.63	6.5	0.691

VAS: visual analogue scale

Table 3. Adverse effects in two treatment groups in patients with acute pancreatitis (AP)

Variables	Paracetamol N (%)	Tramadol N (%)
Allergic reaction (urticaria or itching)	0 (0%)	0 (0%)
Giddiness	0 (0%)	0 (0%)
Nausea and vomiting	0 (0%)	1 (2.5%)
Sedation	0 (0%)	0 (0%)
Others	0 (0%)	0 (0%)

Table 4. Hospital stay in two treatment groups in patients with acute pancreatitis (AP)

	Paracetamol	Tramadol	p value
Number of patients	40	40	
Mean days of hospital stay	4.85	6.8	0.089

The changes in pain scores were calculated by subtracting the mean scores at baseline and 24 hours as pairs. According to the comparison of pain improvements, there was no significant difference between the two groups, Table 2.

Two (2.5%) in the paracetamol group, and one (1.25%) in the tramadol group required the administration of a rescue drug (Inj pethidine). Nausea and vomiting were reported by 1.25% of patients in the tramadol group and it was not reported in the paracetamol group. None of the side effects like sedation, giddiness occurred in patients in tramadol group, Table 3.

Discussion

Our study demonstrated that there was no significant difference between tramadol and

paracetamol with regards to analgesic efficacy in acute pancreatitis. The finding of this study is consistent with the study done by Gülen B et al[7] and various other studies which compared the efficacy of paracetamol with tramadol in various pain patterns.[8,9]

The most common etiology of acute pancreatitis in our study was alcohol (67.5%). It was different from Turkish study where alcohol accounted for only 21.1%, and 73.3% had gallstones and biliary pancreatitis.[6] In another study done by Zheng Y et al from China, alcohol was responsible for only 10% of cases of acute pancreatitis.[10] The predominance of alcohol induced pancreatitis in our study may be attributable to higher number of male patients. The male population are likely to consume more alcohol in our culture, which has been shown by a study by Maharjan P et al.[11]

In our study, one (2.5%) patient each in tramadol and paracetamol group required administration of rescue drug. This is much less than rescue medications required in a study by Gullen B et al. in which four (13.3%) in the paracetamol group, and three (10%) in the tramadol group required administration of a rescue drug.[6] This may be attributable to relatively less number of patients with severe disease (10%) in our study.

Gulen et al. compared the efficacy of both the drugs in the pain management of acute pancreatitis and found them to be at par. They found that one patient in paracetamol group and two patients in tramadol group had nausea and vomiting which was statistically insignificant, and is similar to our findings. In our study, adverse effects of tramadol were also not as high as reported in other studies.[12]

In patients with severe disease (persistent organ failure), who account for about 20% of presentations, mortality is approximately 30%.[13] But there was no mortality in our study. Majority of the patients in our study were relatively young (mean age 39.9 years) and 90% had mild or moderately severe disease; these factors could have led to the improved survival in our patients.

In our study, hospital stay was lesser in patients in paracetamol group as compared to tramadol group (mean hospital stays 4.85 vs 6.8 days), however, this difference was not statistically significant (p=0.089), Table 4. A study by Mohammed S et al. reported that lesser adverse effects with paracetamol use compared to tramadol translates into the lesser duration of hospitalization and hence earlier discharge.[9] However, adverse effects associated with tramadol use was not common in our study.

There are some limitations of our study. This was a single center study with a small sample size and was not blinded. This study showed that tramadol is not superior to paracetamol in relieving pain in acute pancreatitis; however, this does not mean these two drugs have the same efficacy. A larger sample size would be needed to test the hypothesis that intravenous tramadol and paracetamol are equally effective in relieving pain in acute pancreatitis (an equivalence trial). Moreover, study patients had different etiologies of acute pancreatitis, which may also have had an impact on different pain responses to the therapy.

Conclusion

The intravenous paracetamol is an effective alternative to tramadol in pain management of acute pancreatitis.

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Conflict of Interest

None

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None

Author Contribution
All authors made substantial intellectual contributions to the study. RS: Provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revised it critically for important intellectual content, and final approval of the version to be submitted. SK: Supplied the acquisition of data, drafting of manuscript. MS: Supplied the design of study, analysis and interpretation. NP: Responsible for revising the article critically for important intellectual content. AK: Revised the article critically for important intellectual content and gave final approval of the version to be submitted.

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