Severe Acute Pancreatitis: Step-Up versus Step-Down Approach for Pain Control in Initial 72 hours

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ABSTRACT

Background
Attenuating pain in severe acute pancreatitis (SAP) remains a challenge for clinicians specially in first 48-72 hours. Randomized trials are difficult to plan and execute as the pain is very severe and management is frustrating. Moreover, most of the RCTs have focussed on comparison of two drugs rather than comparing the pain regimens as multi-modality treatment.

Objectives
The objective of the study was to compare step-up versus step-down approach of pain management in SAP patients admitted in surgical critical care unit.

Methods
Retrospective analysis of data related to control of pain in SAP was carried out. Patients of acute pancreatitis classified as severe or critical as per Atlanta or determinant based classification were included in the study. Chronic pancreatitis, Etiology other than biliary or alcoholic pancreatitis (BP and AP) and incomplete data entry were the major exclusions. Patients’ files were reviewed, and they were re-classified as SAP. VAS and analgesia requirement were tabulated and analysed. Patients of biliary and alcoholic pancreatitis were divided into two subgroups viz step-up (opioid started later) and step-down (opioid started from the beginning).

Results
Data of 84 patients was calculated and analysed. Mean age of BP patients was significantly less than AP. Males were the major sufferers in AP and females in BP. The mean VAS on arrival was not significantly different between BP and AP. The difference in mean VAS remains insignificant for up to 8 hours of admission, after which, patients with AP started having relief at a faster rate compared to patients with BP. From 4th hour onwards, the fall in VAS was significant more in step down approach. The time when the difference in mean VAS between the step-up and step-down groups of patients with AP was found significant was 10th hour from admission. The difference persisted till 72 hours of observation. Patients of AP responded more favourably to routine analgesics or when the opioids were added later compared to patients of BP. The difference in mean VAS between step down sub-groups of BP and AP did not show significance. An overall comparison of step-up and step-down sub-groups of both BP and AP patients revealed a significant difference in mean VAS from 4th hour onwards.

Conclusion
Patients who followed step-down approach of pain management faired significantly better compared to those who followed step-up approach.

Key words: Biliary pancreatitis–Alcoholic pancreatitis–Visual analog score (VAS)–Fentanyl–Opioid
1 INTRODUCTION
Attenuating pain in severe acute pancreatitis (SAP) remains a challenge for clinicians specially in first 48-72 hours. While mild to moderate pancreatitis usually responds well to pain management protocol as per WHO pain ladder, SAP forms an exception.1–3 Medical literature is full of studies including randomized clinical trials but most of them are poorly designed and focus mainly on establishing the better efficacy of one drug on other. Even the guidelines by professional bodies do not recommend any protocol for the management of pain in SAP. However, the fact that the pain management in SAP can be so frustrating especially in first 48 to 72 hours that adhering to a specific protocol may not be possible for the investigators and this very well explains the absence of good quality RCTs. This study is a retrospective study that tries to compare the outcomes of prevalent practices of pain control in SAP in a critical care setup.

2 OBJECTIVES
The objective of the study was to compare step-up versus step-down approach of pain management in severe acute pancreatitis patients admitted in surgical critical care unit.

3 MATERIAL AND METHODS
The study was planned as a retrospective analysis of data related to pain management of patients admitted due to SAP in surgical critical care unit of the only teaching hospital in Sikkim, a state in north east India, over 2 years between 1st January 2018 to 31st December 2019.

3.1 Inclusion criteria
1. Patients of acute pancreatitis classified as severe as per revised Atlanta classification 2012.
2. Patients of acute pancreatitis classified as severe or critical pancreatitis as per determinant-based classification 2012.

3.2 Exclusion criteria
1. Patients of proven chronic pancreatitis who were or not on treatment and admitted with acute presentation (acute on chronic presentation)
2. Patients of acute pancreatitis other than biliary or alcoholic pancreatitis
3. Incomplete data in the files

4 METHODOLOGY
A patient search was carried out using following terms in the hospital information system between the timeline of study duration: pancreatitis, acute pancreatitis, acute necrotizing pancreatitis, chronic pancreatitis, biliary pancreatitis, alcoholic pancreatitis, acute biliary pancreatitis
Records of all the patients were obtained from the medical records department. The 1st step was to re-confirm the diagnosis and category of severe pancreatitis. Diagnosis of all patients were reviewed. Files of chronic pancreatitis were returned. Remaining patients were reclassified into 3 categories: mild, moderate, and severe (severe and critical) pancreatitis.

Based on how (on or after admission) and what analgesics were given to patients, they were classified into two groups:
Group 1 (step up approach): Initial drugs used were intravenous paracetamol and NSAIDs, alone or in combination and later one or more opioids were added.
Group 2 (step down approach): Opioids were started on admission either alone or in combination with paracetamol and NSAIDs.
The usual practice for all patients with severe pain (irrespective of diagnosis) in surgical ICU is to record visual analog score (VAS) every hour till it falls to 6 or less. For the tabulation and analysis, 2 hourly VAS was chosen for first 12 hours, 4 hourly for next 12 hours, 6 hourly on day 2 and 8 hourly on day 3.

Data was tabulated and analysed using IBM© SPSS© version 23. Categorical data was compared with χ² test and mean were compared with ANOVA.

5 RESULTS
Over a study period of 2 years, 263 patients were admitted in the hospital with a diagnosis of pancreatitis. Out of 263 patients, 97 patients were admitted in surgical critical care unit. Three patients were diagnosed as hyperlipidaemic pancreatitis, 3 patients had features of chronic pancreatitis in CT scan and 7 patients had incomplete data entry. All 13 patients were excluded from the final analysis.

Remaining 84 patients were reclassified into mild, moderate, and severe (including critical) pancreatitis. In surgical ICU, no patient had mild pancreatitis. Only 7 patients (3 in step-up subgroup of BP, 1 each in step-down subgroup of BP and step-up subgroup of AP and 2 in step-down subgroup of AP) had moderate pancreatitis. Fifty-two patients had BP (33 in step-up subgroup and 19 in step-down subgroup) and 32 patients had AP (16 each in step-up and step-down subgroup).

The mean age of the patients was 39.13±7.207 years. The difference between mean age of the step-up and step-down subgroups (of both BP and AP) was not significant (p=0.454). But the mean age of patients in BP was significantly less than that in AP (37.90±7.322 and 41.12±6.651 years, respectively; p=0.046). Female patients were almost 6 months younger (p=0.736) compared to male patients. Male to female ratio of entire study group was 1.1:1 but if

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looked for BP and AP separately, it was 2:1.05 for BP (not significantly different for step-up and step-down subgroups) and 4.3:1 for AP (not significantly different for step-up and step-down subgroups). However, the difference in gender distribution between BP and AP was strikingly significant (p<0.001).

All the patients of BP as well as AP had received intravenous drotaverine 40mg 8 hourly on all 3 days. Before starting fentanyl infusion, a bolus of 0.5 microgram/kg of fentanyl was given to all patients irrespective of the timing of starting fentanyl.

The mean VAS on arrival was not significantly different when compared either between BP and AP or between their sub-groups implying that the patients experience pain of similar severity irrespective of the etiology of pancreatitis. This comparison also ensured that both the groups (BP and AP) as well as their sub-groups (step-up and step-down) were comparable and not significantly different for a further analysis of the retrospective data (p4 in table 1).

The difference in mean VAS remains insignificant for up to 8 hours of admission, after which, patients with AP started having relief at a faster rate compared to patients with BP. The difference which started reflecting from 10 hours onwards persisted till 72 hours of admission (p4 in table 1).

The difference in mean VAS was not significant until 4 hours of admission in both the sub-groups of BP. From 4th hour onwards, the fall in VAS was more in step down approach making the difference significant and this difference was consistent for remaining duration of observation (p1 in table 1).

The time when the difference in mean VAS between the step-up and step-down groups of patients with AP was found significant was 10th hour from admission. The difference persisted till 72 hours of observation (p1 in table 1).

The patients of both BP and AP, who received a step-up approach analgesics, were compared. Patients of AP responded more favourably to routine analgesics or when the step-down approach making the difference significant and this difference was consistent for remaining duration of observation (p1 in table 1).

The findings of the comparison between step-down subgroups of BP and AP contrasted with step-up sub-group. The difference in mean VAS became significant from 8th hour onwards and then persisted throughout (p2 in table 1).

The requirement of intravenous paracetamol remained high in both the sub-groups of BP and AP on day 1 as more than 50% of patients in each subgroup requiring 4g of paracetamol. On day 2, the number of patients requiring 4g paracetamol fell in step-down groups of both BP and AP. The similar trend continued 3rd day also as the number of patients receiving maximum possible dose of paracetamol decreased further (table 2 and 3).

Requirement of intravenous aqueous diclofenac mirrored the requirement of paracetamol. In both the subgroups (step-up and step-down) of BP and AP group, more than 50% of patients required 225mg diclofenac on day 1. Numbers fell more sharply in step-down subgroup of both BP and AP compared to step-up subgroups on subsequent 48 hours (table 2 and 3).

Not all patients were started on fentanyl on admission. Mean duration of starting opioids in the step-up subgroup of BP was 3.63 hours and in AP was 3.36 hours (overall 3.45 hours after admission). The difference in mean duration was not significant (p=0.558). The number of patients who required fentanyl equal to or more than 1.5 microgram/kg/hour was more in step-up sub-group compared to step-down subgroup of both BP and AP. Less number of patients required similar amount of fentanyl in next 2 days. On 3rd day, all 19 patients in step-down subgroup of BP and 10 (62.5%) patients in step-down subgroup of AP were on 0.5 microgram/kg/hour of fentanyl (table 2 and 3).

When the mean doses of analgesics were compared between subgroups, the difference was significant between step-up and step-down subgroups of all the patients (BP and AP together) on day 2 and day 3 for all the three analgesics (table 3).

6 DISCUSSION

Alleviation of pain in patients of pancreatitis is the most important consideration from patients point of view. A lot of work has already been done, so many conclusions reached, and papers critically reviewed, a search for best options to mitigate the suffering from pancreatitis is still on.

Even though the original WHO analgesia ladder was designed to treat chronic pain of malignancy, the more indications were added to cover a wide spectrum of diseases including the acute pain. The modification suggested by Vargas-Schaffer G (2010) to combine one or more steps according to severity of pain holds true for management of acute and severe pain of pancreatitis.(6) However, question still remains unanswered is whether to start with a drug from the lowermost step and then step up either in combination or as a single agent or a higher step drug should be added from the beginning.

Our study compared the most used drugs for pain management in combination with opioids. Pain scores were significantly less on most of the occasions in patients who were started on fentanyl from the beginning (step-down approach). In all these patients, requirement of all the analgesics was reduced compared to step-up group on the 3rd day.

Jakobs R et al (2000) did a randomized study to compare buprenorphine and procaine. In their study, Patients receiving buprenorphine had significant less pain scores and demanded less additional analgesics. They found that the pain reduction was maximum in first two days of starting treatment.(7)

Peiro AM et al (2008) did randomized controlled comparison between morphine and metamizole and found later
Table 1.

<table>
<thead>
<tr>
<th>AnalgesicSub-Drugs groups</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>AP Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>PCM</td>
<td>57.6</td>
<td>20</td>
<td>60.6</td>
<td>15</td>
<td>45.5</td>
<td>11</td>
</tr>
<tr>
<td>&gt;4g/day SD</td>
<td>57.9</td>
<td>8</td>
<td>42.2</td>
<td>3</td>
<td>15.8</td>
<td>8</td>
</tr>
<tr>
<td>DichlofenacSU</td>
<td>57.6</td>
<td>22</td>
<td>66.7</td>
<td>15</td>
<td>45.5</td>
<td>11</td>
</tr>
<tr>
<td>&gt;225mg/day SD</td>
<td>57.9</td>
<td>7</td>
<td>36.8</td>
<td>3</td>
<td>15.8</td>
<td>8</td>
</tr>
<tr>
<td>Fentanyl SU</td>
<td>81.8</td>
<td>13</td>
<td>39.4</td>
<td>0</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>&gt;1.5mcg/kg/hour</td>
<td>57.9</td>
<td>8</td>
<td>42.2</td>
<td>0</td>
<td>11</td>
<td>68.8</td>
</tr>
</tbody>
</table>

Table 2: Patients requiring higher doses of analgesics on all 3 days. Data in parentheses are the number of patients still requiring fentanyl at the rate of 1mcigram/kg/hour. *All 19 (100%) patients were on fentanyl at 0.5mcg/kg/hour. Percentage is calculated out of (n) 33 for BP-SU, 19 for BP-SD, and 16 each for AP-SU and AP-SD. BP, biliary pancreatitis; AP, alcoholic pancreatitis; SU, step-up; SD, step-down. PCM and aqueous diclofenac were given as infusion bolus over 1 hour, fentanyl as continuous infusion after a 0.5microgram/kg bolus in both step-up and step-down subgroups.
to be more effective in pain relief as more patients (75%) achieved pain relief over first 24 hours with a less mean time (10±6.6 hours) compared to former (37.5%, 17±18.3 hours). But their findings were not significant.(8)

Meng W et al (2013) did a systematic review of 8 RCTs with 356 patients and concluded that all of the included RCTs were of low quality and did not favour any particular analgesic agent.(9)

Sadowski SM et al (2015) found that epidural anaesthesia improved arterial perfusion pressure of the pancreatic parenchyma by 43% and also improved VAS significantly over 10 days.(10)

Stigliano S et al (2017) published a review article in which he compared 9 trials related to pain management and concluded that there is lack of clarity about the preferred analgesic and its route of administration. They recommended that the best way to manage pain in acute pancreatitis is to follow the most recent pain guidelines available.(11)

A review article by Schorn S et al (2015) supports the findings of present study that multimodality pain management is more important rather than search for or dependence on a single agent as no single drug has been proven to be better till now.(12) Contrary to classical teaching of adverse effects of opioids on sphincter of Oddi, there is ample evidence to suggest most of the opioids can be safely administered in acute pancreatitis for immediate pain relief.(13) Recently published American gastroenterological association institute guideline on initial management of acute pancreatitis does not provide any guideline or recommendation for management of pain in acute pancreatitis.(14)

7. CONCLUSION

1. Patients of both biliary and alcoholic pancreatitis experience pain of similar intensity when it starts.

2. Pain relief is faster in patients of alcoholic pancreatitis compared to biliary pancreatitis.

3. Fentanyl infusion added from the beginning (step-up approach) helps in bringing down the pain scores significantly faster compared to when it is added later (step-down approach).

4. Good quality randomized control trials are required to formulate the pain management protocol in severe acute pancreatitis.

1. Limitation

2. The study was a retrospective study.

3. Data of only those patients were analysed who were admitted in surgical critical care.

4. No attempt was made to analyse the pain management data in relation to long term outcome (morbidity and mortality).

5. Funding
None

Conflict of interest
None

Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Step Up</th>
<th>Step Down</th>
<th>Total 1</th>
<th>Total 2</th>
<th>p1</th>
<th>p2</th>
<th>p3</th>
<th>p4</th>
<th>p5</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 AP</td>
<td>3557.76±501.890</td>
<td>3578.95±507.257</td>
<td>3576.92±498.867</td>
<td>3583.33</td>
<td>0.983</td>
<td>0.462</td>
<td>0.652</td>
<td>0.881</td>
<td>0.531</td>
</tr>
<tr>
<td>P2 AP</td>
<td>3687.50±478.714</td>
<td>3500.00±516.398</td>
<td>3593.75±598.991</td>
<td>495.968</td>
<td>0.020</td>
<td>0.777</td>
<td>0.522</td>
<td>0.375</td>
<td>0.047</td>
</tr>
<tr>
<td>P3 AP</td>
<td>3606.01±496.198</td>
<td>3421.05±507.257</td>
<td>3538.46±503.382</td>
<td>3547.62</td>
<td>0.025</td>
<td>0.607</td>
<td>0.789</td>
<td>0.361</td>
<td>0.005</td>
</tr>
<tr>
<td>D1 AP</td>
<td>3562.50±512.348</td>
<td>3312.50±478.714</td>
<td>3437.50±508.001</td>
<td>500.717</td>
<td>0.164</td>
<td>0.462</td>
<td>0.652</td>
<td>0.881</td>
<td>0.531</td>
</tr>
<tr>
<td>D2 AP</td>
<td>3455.5±505.650</td>
<td>3157.89±374.634</td>
<td>3346.15±480.384</td>
<td>3321.43</td>
<td>0.031</td>
<td>0.887</td>
<td>0.738</td>
<td>0.612</td>
<td>0.002</td>
</tr>
<tr>
<td>D3 AP</td>
<td>3375.00±500.000</td>
<td>3125.00±341.365</td>
<td>3250.00±439.941</td>
<td>469.831</td>
<td>0.109</td>
<td>0.913</td>
<td>0.789</td>
<td>0.542</td>
<td>0.003</td>
</tr>
<tr>
<td>F1 AP</td>
<td>193.18±57.642</td>
<td>193.42±58.044</td>
<td>193.27±37.415</td>
<td>193.75</td>
<td>0.983</td>
<td>0.462</td>
<td>0.652</td>
<td>0.881</td>
<td>0.531</td>
</tr>
<tr>
<td>F2 AP</td>
<td>201.56±35.904</td>
<td>187.50±38.730</td>
<td>194.5±37.424</td>
<td>37.198</td>
<td>0.020</td>
<td>0.887</td>
<td>0.738</td>
<td>0.612</td>
<td>0.002</td>
</tr>
<tr>
<td>F3 AP</td>
<td>197.73±36.638</td>
<td>177.63±37.170</td>
<td>190.38±37.754</td>
<td>191.07</td>
<td>0.064</td>
<td>0.913</td>
<td>0.789</td>
<td>0.542</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 3. Mean dose requirement of analgesics. P, paracetamol; D, diclofenac; F, fentanyl. Numbers (1,2,3) written against P, D, and F are number of days. Paracetamol and diclofenac in mg/day. Fentanyl is in microgram/kg/hour. Fentanyl in this table does not include 0.5 microgram/kg bolus which all patients received before starting the fentanyl infusion. p-Value has been calculated by comparing mean VAS between step-up and step-down sub-groups within the BP and AP groups (p1), between step-up sub-groups of BP and AP groups (p2), between step-down sub-groups of BP and AP groups (p3), between BP and AP groups (p4) and between step-up and step-down sub-groups of all the patients (p5).
8 REFERENCES


AUTHOR BIOGRAPHY

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