

## A Study to Evaluate the Efficacy and Safety Measures of Opioid Analgesics in Acute Pancreatitis

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### Abstract

**Background:** Acute pancreatitis is a sudden inflammation of the pancreas. Occurs in order of frequency including a gallstone impacted in the common bile duct beyond the point where the pancreatic duct joins it; heavy alcohol use; systemic disease; trauma; and, in minor mumps. Acute pancreatitis may be a single event; it may be recurrent; or it may progress to chronic pancreatitis.

**Objectives:** To study the treatment outcomes of opioid analgesics by using case summaries and discharge medication chart. To assess the safety measures to be followed during the therapy of opioid analgesics. To minimise the ADR'S.

**Method:** A prospective study about the efficacy and safety measurement of opioid analgesics in the treatment of acute pancreatitis was held in a tertiary care hospital.

**Results:** During the study it was observed that many patients have been suffered with severe abdominal pain prior to the treatment with opioid analgesics. This severity of pain is far most better after the treatment.

**Keywords:** Acute Pancreatitis; Opioid analgesics

### Introduction

- Acute pancreatitis is sudden inflammation of the pancreas that may be mild or life threatening but usually subsides.
- The pancreas is part of the gastrointestinal system that makes and secretes digestive enzymes into the intestine, and also an endocrine organ that makes and secretes hormones into the blood to control energy metabolism and storage throughout the body.
- Exocrine pancreas, the portion of the pancreas that makes and secretes digestive enzymes into the duodenum.
- This includes acinar and duct cells with associated connective tissue, vessels, and nerves.
- The exocrine components comprise more than 95% of the pancreatic mass.

- If there is severe pain even in acute pancreatic condition, at least one type of pain reliever or Opioid analgesic such as morphine and its derivatives, are commonly used, but without firm evidence for their effectiveness and safety. The aim of this project is to study the use of opioid analgesics against abdominal pain in acute pancreatitis.

### Symptoms include

- Nausea
- Vomiting
- Diarrhoea
- Loss of appetite
- Rapid pulse
- Abdominal Pain during coughing and deep breathing

- Tenderness when the abdomen is touched
- Fever and a temperature of at least 100.4°F
- Jaundice.

### Need of study

- Pancreatitis has emerged as a major health problem worldwide, with serious health related and socio-economic impacts on individuals and population alike. Due to globalization, industrialization, increasing urbanization results in the overall growth of pancreatitis. The high production and consuming of alcohol by the people all over the world will result in corresponding serious morbidity, disability, diminished life expectancy, and reduced quality of life, loss of human and social capital as well as individual and national income. Pancreatitis is such a condition where the chronic condition definitely leads to loss of life. This is mainly because of the high consumption of alcohol and in some cases sudden quit of consumption may also leads to such a condition of pancreatitis.
- Hence the treatment pattern involves the management of major symptom, abdominal pain by using opioid analgesics. And the need of this study is to manage the pain by using the best opioid analgesic in the treatment, that shows immediate action with very less ADRs.

### Literature Review

- D Hariharan, A Saied and HM Kocher conducted a study on "Analysis of mortality rates for pancreatic cancer across the world" concluded that Pancreatic cancer is known to affect older individuals, as only 10% of patients develop this condition below the age of 50 Smoking is the strongest environmental risk factor. A meta-analysis of cohort and case-control studies shows a significant correlation between cigarette smoking and pancreas cancer; the risk increasing with the number of cigarettes smoked explain the rise and fall of pancreatic cancer-related mortality in different parts of the world, though some insights may be gained from this preliminary study indicating that smoking may affect the changes seen. Additionally, the change in use of various diagnostic modalities may explain the differences seen in our study. The epidemiology of pancreatic and related cancers deserves a more in-depth study in the near future when more data become available.

- Peter A. Banks, MD, Faculty,<sup>1</sup>Darwin L. Conwell, MD, MS, and Phillip P. Toskes, MD, conducted a study on "The Management of Acute and Chronic Pancreatitis" and concluded that Chronic pancreatitis causes irreversible scarring of the pancreas, resulting from prolonged inflammation. The most accepted hypothesis regarding the pathogenesis of chronic pancreatitis is the sentinel acute pancreatitis event (SAPE) hypothesis, in which an initial insult or injury to the pancreas results in acute pancreatitis. A migration of satellite cells and inflammatory reactions subsequently occurs. Repeated and prolonged pancreatic inflammation leads to the accumulation of collagen and matrix proteins. Cytokines such as tumour growth factor beta (TGFβ) cause fibrosis and scarring of the pancreatic tissue, which can result in decreased pancreatic function.
- Ari Garber, Catherine Frakes, Zubin Arora, and Prabhleen Chahal conducted a study on "Mechanisms and Management of Acute Pancreatitis" concluded that Acute pancreatitis remains a frequent cause of hospital admission necessitating a multi-pronged approach for the diagnosis and management. While its antecedents remain multifactorial, as are the number of scoring systems that define severity, treatment is predominantly geared toward supportive care with advanced endoscopic adjuncts (in the setting of choledocholithiasis, symptomatic pseudocysts, or walled-off pancreatic necrosis) and early surgical intervention (i.e. cholecystectomy in the setting of an index admission for gallstone pancreatitis) utilized when clinically indicated.
- Vege Santhi Swaroop, MD; Suresh T. Chari, MD; Jonathan E. Clain, MD conducted a study on "Severe Acute Pancreatitis" and concluded that In the United States, approximately 210 000 patients admitted to hospitals each year with acute pancreatitis, about 20% have severe acute pancreatitis (SAP), and primary care physicians and internists are often the first clinicians to care for these patients. In contrast to mild acute pancreatitis, which has a mortality rate of less than 1%, the death rate for SAP is much higher: 10% with sterile and 25% with infected pancreatic necrosis. Hospitalization for patients with SAP may extend beyond 2 weeks and frequently involves an intensive care unit (ICU) stay.

- B. Gloor, C. A. Müller, M. Worni M., E. Martignoni, W. Uhl, Dr M. W. Büchler conducted a study on “Late mortality in patients with severe acute pancreatitis” concluded that early deaths in patients with severe acute pancreatitis are rare, mainly as a result of modern intensive care treatment. Nine of the ten deaths occurred more than 3 weeks after disease onset. Infection of pancreatic necrosis was the main risk factor for death. 2001 British Journal of Surgery Society Ltd [1-6].

### Aim of the Study

To make a detail study on the efficacy and safety measurement of opioid analgesics against abdominal pain in acute pancreatitis.

### Objectives of the Study

- To study the treatment outcomes of opioid analgesics by using case summaries and discharge medication chart.
- To assess the safety measures to be followed during the therapy of opioid analgesics.
- To minimise the ADR'S.

### Materials and Methods

**Study design:** It is a prospective observational study.

**Study site:** The study was conducted in Santhiram Medical College and General Hospital, Nandyal.

**Study period:** The present study was carried out for a period of six months from June-2019 to November -2019.

**Institutional ethical committee (IEC):** After the approval of Institutional Human Ethics Committee, at Santhiram Medical College and General Hospital, Nandyal this study was initiated

**Sample size:** During the study period of six months of this study, the total sample size was 130 patients.

### Study criteria

#### Inclusion criteria

- Patients with raised lipase and amylase.
- Patients showing features of acute pancreatitis in CECT (Contrast enhanced computed tomography).
- Patients with age 18 - 59 years.
- Patients with suspected gastric symptoms.

#### Exclusion criteria

- Patients with age above 60 years.
- Participants who are unwilling to join the study.
- Pregnant women.
- Patients who are sensitive towards opioid analgesics.

#### Source of data

- Data is collected from all the peptic disease patients who are visiting the Gastroenterology department of the Santhiram General Hospital, Nandyal.
- Data is collected by using specially designed patient data collection forms.

#### Method of collection of data

- The necessary information was collected by interviewing the patients using the following annexure.
- Assessment of pain severity using WONG BAKER's Scale
- Annexure-I (Patients demographic characteristics proforma)
- Annexure-II (peptic diseases health assessment questionnaire)
- Annexure-III (informed consent forms).

#### Annexure-I

This annexure was self-prepared, structured data collection form used to collect the demographic details of the recruited subjects. It includes age, sex, education level, place of living etc.

#### Annexure-II

This annexure was standard questionnaire form, structured data collection form used to collect the signs and symptoms and various co morbid conditions of peptic disease patients like Hypertension, Smoking, Alcohol, Infectious disease.

#### Annexure-III

This annexure includes the patient informed consent form that the form used for involvement of the patient in the study this form is in Telugu and English languages.

### Results

The total population selected for this study is 130 patients and selected both male and the female patients of three different age groups i.e., 18 - 35, 36 - 45 and 46 - 60.

Age (in years)	Males (n)	Females (n)	Percentage	
			M	F
18 - 35	48	16	36.92%	12.30%
36 - 45	44	8	33.84%	6.15%
46 - 60	8	6	6.15%	4.61%
Total (n)	100	30	76.92%	23.08%

**Table 1:** Age wise gender distribution.

**Figure 2**

**Figure 3**

**Figure 1**

**Figure 4:** Amylase secretion range in male patients.

Habits	18 - 35Y		36 - 45 Y		46 - 60 Y		Total		Percentage	
	M	F	M	F	M	F	M	F	M	F
Alcohol (1)	2	0	2	0	0	0	4	0	3.07	0
Smoking (2)	6	0	0	0	0	0	6	0	4.61	0
Chewing tobacco (3)	0	0	0	2	0	4	0	6	0	4.61
Both 1 and 2	38	0	36	0	4	0	78	0	60	0
All three	0	0	6	0	4	0	10	0	7.69	0
Nil	2	16	0	6	0	2	2	24	1.53	18.46
							N = 100	N = 30	N = 76.92%	N = 23.08%

**Table 2:** Co-morbid conditions of patients.

Figure 5: Amylase secretion range in female patients.

Figure 6: Lipase secretion range in male patients.

Amylase Range (IU/L)	18 - 35 Y.		36 - 45 Y.		46 - 60 Y.		Total		Percentage		
	M	F	M	F	M	F	M	F	M	F	Total
200 - 500	14	8	8	0	2	2	24	10	18.46	7.69	26.15
500 - 1000	30	6	36	8	6	4	72	18	55.38	13.84	69.22
> 1000	2	0	0	0	0	0	2	0	1.53	0	1.53
Nil	2	2	0	0	0	0	2	2	1.53	1.53	3.06

Table 3: Range of amylase enzyme secretion in patients.

Lipase Range (IU/L)	18 - 35 Y.		36 - 45 Y.		46 - 60 Y.		Total		Percentage		
	M	F	M	F	M	F	M	F	M	F	Total
200 - 500	26	14	32	4	8	4	66	22	50.76	16.92	67.68
500 - 1000	12	0	8	4	0	2	20	6	15.38	4.61	19.99
> 1000	0	0	2	0	0	0	2	0	1.53	0	1.53
Nil	10	2	2	0	0	0	12	2	9.23	1.53	10.76

Table 4: Range of lipase enzyme secretion in patients.

Figure 7: Lipase secretion range in female patients.

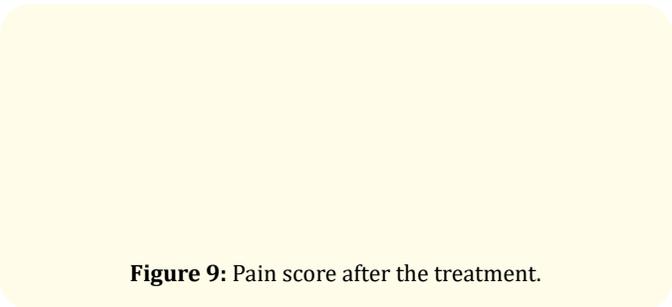
Figure 8: Pain assessment before treatment.

Pain type	Wong bakers Scale	18 - 35yrs		36 - 45 yrs		46 - 60 yrs		Percentage (%)		
		M	F	M	F	M	F	M	F	Total
Hurts even more	6	18	10	6	2	0	0	18.46	9.23	27.69
Hurts whole lot	8	26	6	18	6	4	4	36.92	12.3	48.95
hurts worst	10	4	0	20	0	4	2	21.53	1.53	23.06

Table 5: Pain assessment before treatment.

Pain type	Wong bakers Scale	18 - 35 yrs		36 - 45 yrs		46 - 60 yrs		Percentage (%)		
		M	F	M	F	M	F	M	F	Total
No hurt	0	38	14	26	4	0	2	49.23	15.38	64.61
Hurts little bit	2	6	2	6	2	4	4	12.30	6.15	18.45
Hurts little more	4	4	0	4	2	2	0	7.69	1.53	9.22
Surgery		-	-	8	-	2	-	7.69	0	7.69

Table 6: Pain assessment after treatment with tramadol.



Opioids and dose	Severity of pancreatitis	Interactions/compliances	Efficacy of action	Formulation cost	
Morphine (15 - 30 mg)	Chronic	++	+++	Oral	++
	Moderate	+	+++		
	Mild	+	+++		
Tapentadol (50 - 100 mg)	Chronic	++	+	Oral	+++
	Moderate	+	+++		
	Mild	Nil	+++		
Tramadol (50 - 150 mg)	Chronic	Nil	++	Oral	+
	Moderate	Nil	+++		
	Mild	Nil	+++		

Table 8

Discussion

The general treatment pattern for acute pancreatitis is followed with opioid analgesics, proton pump inhibitors, anti-emetics, anti-biotics, and anti-diabetic drugs as follows.

Category	Example	Comments/remarks
Analgesics (Opioid)	Tramadol, Morphine, Tapentadol.	Pain reliever
Proton pump inhibitor	Pantoprazole, rabeprazole, omeprazole	To maintain the acidic PH in stomach
Anti emetic	Ondansetron	To control the emesis
Antibiotic	Cefixime, Amoxicillin.	Antimicrobial
Anti diabetic	Metformin, glimepiride	To maintain the insulin balance

Table 7

To assess the safety, efficacy among available and practicing three types of opioid analgesics i.e., Morphine, Tapentadol and Tramadol, we followed the qualitative comparison study of opioid analgesics on close observation with patient treatment on three types of analgesics, prescribed range of dose with severity and condition of the diseases. The observations of compliances, efficacy and cost comparison are based on strong/ high +++, moderate++ and weak/low + are placed in table.

From the above table, The drug-drug interactions/compliances, effectiveness and cost of drugs are observed, in that the response of morphine in chronic, moderate and mild conditions of diseases are good with various dose levels and the compliances are noted are constipation and dry mouth.

The Tapentadol has shown moderate drug interactions in chronic conditions, low interactions in moderate conditions and no interactions were seen in mild conditions. This drug is available only in the form of tablets, whose cost is very high when compared to morphine and Tramadol.

As a third choice of drug Tramadol was chosen and examined in all the three conditions and found that It did not show any drug-drug interactions and the result of efficacy was high and satisfactory in all conditions. The cost of drug is very cheaper when compared to those of Morphine and Tapentadol.

It is concluded that Tramadol is safe and effective with lower drug-drug interactions at economical rate when compared to stated opioid analgesics.

The treatment for acute pancreatitis was carried out with Tramadol and noticed the following better results:

- From the table, it was observed that, the total population selected for this study was 130 patients. This sample size includes both the male and the female patients, of three different age groups i.e. (18 - 35, 36 - 45, and 46 - 60).
- It is observed from above table that 76.92% of male and 23.08% of female patients were identified with acute pancreatitis at SRMC&GH for the study. In this 18 - 35 age group and 36 - 45 age group of male are suffering with 36.92% and 33.84% respectively than the female 12.30% of 18 - 35 age groups.

### Conclusion

Our study to evaluate the efficacy and safety measures of opioid analgesics in acute pancreatitis concluded that:

- It is noted that the possibility of acute pancreatitis is more predominant in 18 - 35 age group in both sex, in that male is more.
- The majority of patients are with social habits of both smoking and alcohol consumption and some are with tobacco chewing.
- The observations indicate that diabetes is a more severe comorbid condition that causes acute pancreatitis when compared to hypertension and asthma.
- The examination of both amylase and lipase secretions are independent of acute pancreatitis.
- It is concluded that Tramadol is safe and effective with lower drug-drug interactions at an economical rate when compared to stated opioid analgesics when compared to those of Morphine and Tapentadol.
- From the study it was also concluded that patients with no comorbidities are completely cured denoting the pain score of "0" (NO HURT).
- It can be understood that the drug i.e. TRAMADOL given was very effectively shown its function.
- The patient counseling also helps more for the patients on habits and for better treatment methods to cure and avoid the surgery cases in few patients.

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