ORIGINAL RESEARCH PAPER

Volume - 12 | Issue - 06 | June - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"EVALUATION OF EFFICACY OF ANALGESIA WITH OPTIMIZED PHARMACOTHERAPY AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC PANCREATITIS – A PROSPECTIVE, SINGLE CENTRE OBSERVATIONAL STUDY"

General Medicine

Dr Sanjay Gedam — Professor, Department of Pharmacology, Netaji Subhash Chandra Bose Medcial College, Jabalpur, Madhya Pradesh, India

Dr Pankaj Asati — Associate Professor, Department of Medicine, Netaji Subhash Chandra Bose Medcial College, Jabalpur, Madhya Pradesh, India

Dr Krunal Chaudhari* — PG Resident, Department of Pharmacology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India. *Corresponding Author

ABSTRACT

Pain is the most common symptom in chronic pancreatitis (CP) with a major impact on quality of life. Present study was planned with aim of to determine the efficacy of optimized pharmacotherapy for Analgesia & Quality of Life (QoL) in patients with Chronic Pancreatitis. Total 67 patients with CP were analysed on base line, 3 months, 6 months follow up with VAS score for pain and, SF-36 & PANQOLI scores for quality of life. There were significant changes in VAS score at 3 and 6 moths follow up as well as SF-36 and PANQOLI were statistically significant an both visit ($p<0.001$). It could be concluded from the present study that if started early, significant pain relief and improved quality of life is achieved in maximum patients with optimized pharmacotherapy.

KEYWORDS

Chronic Pancreatitis, Quality of Life, Visual Analogue Score, SF-36 score, PANQOLI score

INTRODUCTION:

Chronic pancreatitis (CP) is defined as "A disease process characterized by irreversible damage to pancreas as distinct from the reversible changes noted in acute pancreatitis. The condition is best defined by the presence of histological abnormalities, including chronic inflammation, fibrosis, and progressive destruction of both exocrine and eventually endocrine tissue." [1] Prevalence of chronic pancreatitis in Western countries is 10-15 while in India it is 125 cases per 100,000 population.[2] It commonly affects young adults with a higher incidence in males. Chronic pancreatitis is seen more in males than females with male/female ratio of 4:1.[3] CP is also associated with pancreatic insufficiency, both endocrine and exocrine [4,5], which develops in 50% and 80% of patients within 5 years, respectively. CP is related to several causative factors, most notably alcohol toxicity. Other factors such as genetics, anatomic abnormalities and autoimmunity also play a role [6]. Alcohol is the most common etiological factor followed by Idiopathic pancreatitis in India. Nearly 2/3rd of the patients has history of heavy alcohol consumption for over a decade.[7]

Chronic pancreatitis is the end result of many etiological factors which cause pancreatic injury.[1] Abdominal pain is the most common presenting symptom of CP which is caused due a multitude of reasons including recurrent or chronic inflammation of parenchyma, localized complications, or neurological mechanisms with nervous system changes. The other manifestations are steatorrhea and diabetes mellitus.[8] It is crucial to treat chronic pancreatitis as soon as possible, because repeated episodes of inflammation can cause irreversible damage and make pharmacotherapy less effective. [1] In current practice, patients with CP are managed by a conservative step-up practice. The first step is medical management, ranging from pancreatic enzymes and mild analgesics to opioids. When medical management fails, the next step is usually endoscopic intervention.

Surgical intervention is kept as an option of last resort when other treatments have failed and the severity of disease has increased substantially and pain becomes unmanageable [9,10]. Also, pancreatic enzyme replacement therapy (PERT) can be used for pain relief. PERT inhibits meal related pancreatic secretion which is believed to help in pain management. [14] Along with them, antioxidants are preferred too. Antioxidants corrects the oxidant-antioxidant balance which has occurred due to oxidative stress. The antioxidants halt the inflammation and provide a significant pain relief. [14] The pharmacotherapy of CP is targeted towards alleviating pain and improving QoL. The mainstay of treatment includes Analgesics, Pancreatic enzymes, and Antioxidants.[13]

So, present study was planned with aim of to determine the efficacy of optimized pharmacotherapy for Analgesia & Quality of Life (QoL) in patients with Chronic Pancreatitis.

MATERIALS AND METHODOLOGY:

This prospective observational study was carried out after obtaining ethical approval from Institutional Ethical Committee in the department of Medicine, Gastroenterology OPD and in Department of Pharmacology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, between March 2021 to September 2022. This present study was conducted in accordance of International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, catering for all its precautions.

The patients were enrolled with following inclusion and exclusion criteria. Inclusion criteria were patient more than 14 years and less than 65 years of age of either gender, patient willing to attend continuous follow-up in same OPD for a period of 6 months and excluded when patient was pregnant and lactating women, patient less than 14 years & more than 65 years of age of either gender, patient not providing informed consent, patient who are drug addicts/dependants, patient with history of /or Current Renal Insufficiency, patient with history of Bronchial Asthma, patient with severe acute liver disease, patient having Gout, patient diagnosed with Crohn's Disease.

Prescriptions were collected from Gastroenterology OPD under Medicine department out of which those fulfilling the inclusion and exclusion criteria were included in study. The relevant data on demographics and pharmacotherapy prescribed of all patients was collected from the OPD slip. After obtaining patient consent, all of the patient underwent a detailed questionnaire-based evaluation which included SF-36 and PANQOLI on their 1st visit. All of the patient described their pain score on Numerical Pain rating scale on their 1st visit. At 3-month follow-up visit, all patient's drug compliance was noted with respect to the pharmacotherapy prescribed. A detailed questionnaire-based evaluation of SF-36 and PANQOLI was done and pain score was noted on numerical pain rating scale. Similarly at 6-month follow-up visit, drug compliance with respect to pharmacotherapy prescribed, evaluation of SF-36 & PANQOLI and pain score was noted. The SF-36 questionnaire scores (PCS & MCS) were described as mean of the sum of all 36 items in questionnaire. The PANQOLI score was described as mean of sum of all the 18 items in questionnaire. The data collected was analysed further to assess the outcome of pharmacotherapy with appropriate tools. Data collected were Demographics (age, gender), etiology of Chronic Pancreatitis, duration of Chronic Pancreatitis, pharmacotherapy prescribed and patients compliance to therapy, study variables Pain Score, PCS & MCS of SF-36 and PAN-QOLI Score in the following manner: -

- Change in Pain Score values at 3 month & 6 months from baseline
- Change in PCS & MCS values at 3-month, 6 months from baseline
- Change in PANQOLI score values at 3-month, 6 months from baseline

Statistical Analysis:

The data was stored, segregated, processed with the help of computer software MS Excel. Statistical analysis was conducted using Data analysis tool pack, add on feature with MS Excel. The data collected at 0 month were used as the baseline against which changes during therapy were compared. All characteristics were summarized descriptively. For categorical data, the number and percentage were used in the data summaries. To compare change of pain score at 0-month, 3 months & 6 months, paired T test was used. P value of <0.05 was considered significant.

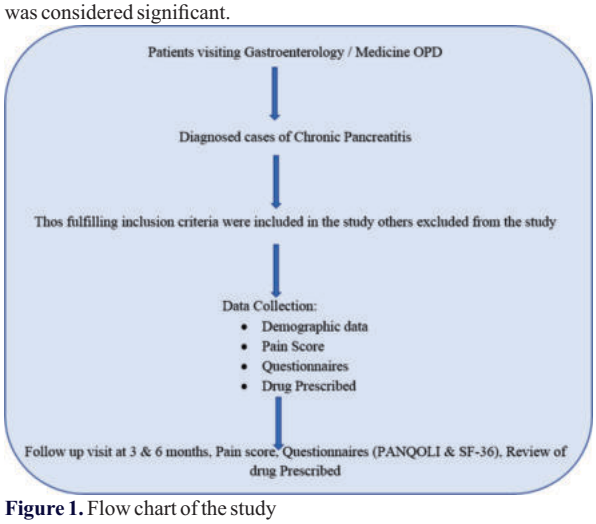

Figure 1. Flow chart of the study

RESULT:

A total of 81 prescriptions were collected of which 72 were enrolled in study after exclusion criteria. Of the 72, 1 patient died and 3 patients were lost to follow-up at 3 month and 1 patient lost to follow-up at 6 months. So, a total of 67 patients health status was analyzed for the study.

Table 1. Age and Gender wise distribution of patients with chronic pancreatitis

Age group	Male	Female	Total	Percentage (%)
<20	3	0	3	4.5
21-30	15	7	22	32.8
31-40	19	4	23	34.3
41-50	12	2	14	20.9
>51	4	1	5	7.5
Total	53 (79.1%)	14 (20.9%)	67 (100%)	100

As per table no 1. illustrates that out of 67 patients, 53 (79.1 %) were Male and 14 (20.9%) were Female. The Male/Female ratio was 3.7:1. The male patients were affected more than female patients in Chronic Pancreatitis. Maximum number of patients belonged to the age group of 31-40 year: - 23 patients (34.3%), followed by 21-30 year: - 22 patients (23.2%). The youngest patient was 19 years and oldest patient 57 years with a mean age of 34.82 ± 9.8. Most patients presented in their 4th decade of life. (Table no.1)

The etiology of Chronic Pancreatitis as Alcoholic in 42 patients (62.7 %) followed by Idiopathic Pancreatitis in 25 patients (37.3%). (Fig.2) The duration of Chronic Pancreatitis from minimum 3 months to maximum 36 months with a mean of 8.19 ± 4.5 months.

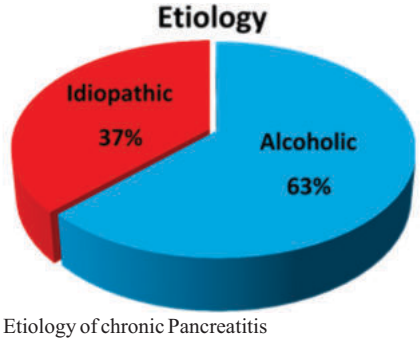

Figure 2. Etiology of chronic Pancreatitis

Table 2. Pharmacotherapy prescribed ant its compliance at baseline, 3 months and 6 months follows up.

Pharmacotherapy Prescribed	Baseline	3 months	6 months
FDC	67 (100%)	67 (100%)	67 (100%)
PERT	67 (100%)	65 (93%)	64 (95.2%)
Anti-oxidant	56(83.60%)	55 (82.10%)	50 (74.63%)
Drug Compliance	67 (100%)	55 (82.10%)	58 (86.6%)

Data are expressed as n (%)

As per table no. 2 illustrates that FDC (Paracetamol-325 mg + Tramadol- 37.5 mg) was prescribed to all 67 (100%) patients at Baseline (1st visit), 3 month(1st follow up) & 6 month (2nd follow up) respectively; PERT (Pancreatic Enzyme Replacement therapy) was prescribed to all 67 (100%) patients at Baseline (1st visit) , 65 (97%) patients at 3 month (1st follow up) & 64 (95.52%) patients at 6 month (2nd follow up) respectively; and Antioxidants were prescribed to 56 (83.6%) patients at their Baseline (1st visit), 55 (82.1%) patient at 3 month (1st follow up) & 50 (74.63%) patients at 6 month (2nd follow up) respectively. 55 (82.1 %) patients showed compliance to prescribed pharmacotherapy at 3 months (1st Follow-Up) while 58 (86.6%) patients were compliant to prescribed pharmacotherapy at 6 months (2nd follow-up). (Table 2)

Table 3. Pain score according to Visual Analogue Scale

Pain Score	Baseline	3 months	6 months
1	0	0	4 (6%)
2	0	1 (1.5%)	7 (10.4%)
3	0	1 (1.5%)	24 (35.8%)
4	1 (1.5%)	10 (14.9%)	17 (25.4%)
5	0	23 (34.3%)	6 (9%)
6	8 (11.9%)	20 (29.9%)	4 (6%)
7	28 (41.8%)	8 (11.9%)	4 (6%)
8	23 (34.3%)	4 (6%)	1 (1.5%)
9	7 (10.4%)	0	0
10	0	0	0

Data are expressed as n (%)

Around 74% of patient had a pain score of 8(34.3%) & 7(41.8%) on their 1st visit. Around 64% of patient had a pain score of 5(34.3%) & 6(29.9%) on their 1st follow up visit at 3 month which was 7 & 8 in 74% patient at baseline. Around 70% of patient had a pain score of 2(10.4%), 3(35.8%) & 4(25.4%) on their 2nd follow up visit at 6 month which was 5 & 6 in 64% patient at 3 month follow up. (Table 3)

Table 4. Comparison of various score

Score	Baseline	3 months	6 months	P value
Vas Score	7.39 ± 0.94	5.49 ± 1.20	3.7 ± 1.54	<0.001
SF-36 PCS	24.83 ± 9.28	43.64 ± 13.00	62.06 ± 15.83	<0.001
SF-36 MCS	19.43 ± 8.33	38.04 ± 13.28	57.33 ± 17.14	<0.001
PANQOLI	32.43 ± 8.67	49.42 ± 10.80	66.55 ± 13.53	<0.001

Data are expressed as Mean ± SD.

There was a significant change in pain severity at 3- and 6- month follow-up compared to pre-treatment pain scores ($p< 0.001$, $p< 0.001$). The mean of MCS Baseline, 1st follow up (3 month) & 2nd follow up (6 month) were 19.43, 38.04 & 57.33 respectively ($p<0.001$). (Table 4) A total of 9 ADRs were reported. (Table 5.1 & 5.2)

Table 5.1 & 5.2 Adverse Drug Reaction reported during study duration with causality

ADR	FDC	PERT	Antioxidant
Constipation	3(33%)	0	0
Headache	1(11%)	1(11%)	0
Dizziness	1(11%)	0	1(11%)
Nausea	1(11%)	0	1(11%)
Total	6(66.7%)	1(11%)	2(22%)

Drugs	Certain	Probable	Possible	Unlikely
FDC	0	4	2	0
PERT	0	1	0	0
Antioxidants	0	1	1	0
Total	0	6	3	0

DISCUSSION:

In this prospective study, we observed the gender classification, age-wise sex distribution, etiology, duration of chronic pancreatitis, drugs prescribed, compliance to prescribed drugs, pain score, PCS & MCS of QOL and PANQOLI score over a period of 6 months.

The mean age of presentation in our study was 34.82 ± 9.8 years which correlates well with most other studies. Most patients presented in their 4th decade (31-40 years) of life like previous study. [11] The number of male patients (79.1 %) are predominant over female (20.9 %) which is similar with previous studies. [11-13] In our study, there were 53 males and 14 females, giving a sex ratio of 4:1, in favour of males. The sex ratio of 4:1 was also confirmed in a study conducted by Goulden MR et al,.[3] In our study of 67 patients, the etiology of chronic pancreatitis was Alcohol in 42(62.7%) and idiopathic in 25 (37.3%) which is similar to a study by Garg PK showing that etiology of CP as Alcohol (35.11%) is more than Idiopathic (12.90%). [2] Other studies also support our finding that etiology of chronic pancreatitis is alcoholic and it is more than idiopathic in nature. [7,14-16]

In the present study, compliance to the prescribed medical therapy was noted good with 82% at 3 month and 87% at 6 months. It shows that 82 % patients at 3 months follow up and 87% patients at 6 months follow up were consuming their prescribed medicines on time and as suggested which is similar to the study done by D'Haese et al. where the compliance was 83.7% at 3 months.[17]

A combined optimized drug therapy of analgesics FDC (Paracetamol 325 mg & Tramadol- 37.5 mg), pancreatic enzymes and antioxidants were given at baseline, 3 month & 6 months. In our study, the drug therapies were very effective in controlling the severe pain associated with chronic pancreatitis. The mean pain scores were reduced from over 7.39 ± (0.94 SD) at baseline to 5.49 ± (1.20 SD) at 3 months follow up & 3.7 ± (1.54 SD) at 6 month follow up on a numeric pain rating scale of 0 to 10 which is similar to study the done by Clive H et al. where the pain reduced significantly from 75 ± 19 to 8 ± 13 on visual analogue pain scale after treatment with tramadol.[18] Other studies by Bhasin DK, Savage SR et al., Nusrat S et al. and A.M. Drewes et al. also showed similar results and were comparable to our study. [19-22] In another randomized control trial conducted by Braganza JM, pancreatic enzyme replacement therapy had shown significant relief in pain in CP patients which is similar to present study. [23]

In present study, we observed that mean of PCS and the mean of MCS before starting of medical therapy, at 3 month follow up, and at 6 months follow up. Both this sub scores showed a significant (P<0.001) improvement in Quality of Life after medical therapy over the period of study (Table 5). Our observation were similar to the study done by D'Haese et al., where they concluded that PERT (pancreatic enzyme replacement therapy) demonstrated significant improvement in quality of life of patients with CP. [17] Another study by Shalimar S et al., showed similar results which showed that optimized medical therapy which included pancreatic enzyme achieved significant pain relief in 52.1% patients of chronic pancreatitis which improves quality of life.[24] Probable reason for our result may be that inhibition of meal related pancreatic secretion may help in pain management. Delivery of pancreatic enzymes (especially proteases) destroys the intestinal CCK releasing factor thereby overcoming the hyper stimulatory state that exists in chronic pancreatitis.[19] another reason to reduce pain and increase Quality of life is the correction of oxidant-antioxidant balance halts the inflammation and provide pain relief which can be done by antioxidant supplementation.[19]

The mean PANQOLI score is significantly increased to 49.42 ± 10.80 at 3 month follow up whereas it increased to 66.55 ± (13.53 SD) at 6 month follow up. This shows a significant (P<0.001) improvement in quality of life in chronic pancreatitis. The higher the score better is the quality of life. A similar study by Kirk G et al. evaluated that medical therapy which included Antioxidants was associated with significant improvements in quality of life in terms of pain, physical and social functioning, and general health perception. [25] In our study, a total of 9 adverse drug reactions (ADR) were reported. Out of 9 ADRs, 3 ADRs (33%) of constipation and 1 ADR each of headache, dizziness & nausea were reported due to FDC (Acetaminophen + Tramadol); 1 ADR of headache was reported due to PERT and 1 ADR each of dizziness & nausea due to Antioxidants were reported which is similar to study by Smith W et al. [18]

Limitation and Recommendation:

It was a single centre, observational, prospective, 18-month duration study where selection of sample size was done on the basis of exclusion and inclusion criteria which might not have been adequate. Adherence to pharmacotherapy was self-reported and thus could have led to subjective bias. The limitations of the present study were lack of response comparison among group. It might be difficult to ascertain whether the response was due to analgesics or pancreatic enzymes supplementation or antioxidants. Studies with large sample size and longer follow-up should be conducted among the comparison group. The routine use of quality-of-life questionnaires to assess the well-being of patients with chronic pancreatitis should be practiced.

CONCLUSION:

It could be concluded from the present study that significant pain relief and improved quality of life is achieved in maximum patients with optimized pharmacotherapy.

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