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EVALUATION OF COX-2 INHIBITORS IN PREVENTION OF SEVERE FORM OF ACUTE PANCREATITIS

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Abstract

Introduction: Gallstones and alcohol misuse activate damaging enzyme cascades, causing acute pancreatitis. Categorization systems use criteria such as SIRS, organ failure, and necrotizing pancreatitis to determine the severity. COX-2 inhibitors may suppress inflammation and prevent severe manifestations. Antibiotics, ERCP, procedures, and supportive care are used. For better survival, severe acute pancreatitis requires novel gut barrier failure and inflammatory response prevention.

Aim and objectives: This study evaluates the efficacy of COX-2 inhibitors in avoiding severe acute pancreatitis and assessing their influence on illness severity and outcomes.

Method: In a prospective single-center randomized controlled trial conducted at the Department of General Surgery during the period of one year, patients with acute pancreatitis (AP) were randomly assigned to either a COX-2 inhibitor group or a control group. Patients in the COX-2 group received parecoxib and celecoxib, while the control group received placebos. Assessment criteria included APACHE-II, SIRS, and OF (1) scores, self-assessed abdominal pain ratings, and inflammatory markers. Inclusion criteria involved age, confirmed AP diagnosis, APACHE II score, and written consent, while exclusion criteria included pregnancy, severe chronic diseases, drug allergies, and psychosis. Follow-up study was done and organ failures, occurrence of severe acute pancreatitis and secondary outcomes were assessed and analyzed statistically between the groups anc conclusion was drawn.

Result: There was a good match in terms of baseline characteristics between the control and Cox-2 groups in this trial of 110 people. The death rates were similar in both groups, while the Cox-2 group had a greater incidence of SAP. Reducing organ failure and improving secondary outcomes may be associated with Cox-2 treatment. To learn how Cox-2 inhibitors affect acute pancreatitis disease severity and patient outcomes, more research is necessary.

Conclusion: Using COX-2 inhibitors sequentially in SAP patients reduced the incidence of SAP, decreased TNF-a and IL-6, and increased the cost-effectiveness of symptom treatment.

Keywords: "COX-2 inhibitors (C1COX-2-Is)", SAP, harms cells, disrupting enzyme.

INTRODUCTION:

Acute pancreatitis, an abrupt inflammatory ailment of the pancreas, manifests suddenly, marked by the activation of digestive enzymes within the pancreatic tissue itself. This activation triggers damage not only to the pancreas but also to adjacent organs. Its clinical presentation often involves intense abdominal pain and elevated blood levels of specific pancreatic enzymes like amylase and lipase, alongside confirmatory findings on imaging studies. Root causes of this condition encompass a spectrum—from gallstones, alcohol overuse, and medication side effects to various other contributing factors [1,2].

Acute pancreatitis stems from varied triggers like gallstones and alcohol abuse, leading to pancreatic enzyme activation. Gallstones obstruct ducts, prompting enzyme reflux, while alcohol directly harms cells, disrupting enzyme function. Triggered by factors like ischemia or hypercalcemia, early trypsinogen activation sparks a destructive enzyme cascade, causing self-digestion of the pancreas. This process, intensified by recruited neutrophils, results in tissue damage and robust inflammation, hallmarking severe acute pancreatitis [3-5].

Acute pancreatitis manifests across a spectrum of severity, ranging from mild, self-resolving cases to severe forms carrying substantial health risks. Severity assessments, such as the "Revised Atlanta Classification (RAC)" and the "Determinants-Based Classification (DBC)", categorize the condition based on clinical criteria and complications, aiding in prognosis prediction and treatment pathways. Severe acute pancreatitis involves enduring organ failure, while milder cases lack such complications. These classification systems serve as invaluable tools, precisely characterizing disease progression and facilitating comparisons among patients and treatment approaches in diverse clinical settings [6-11].

The severity of acute pancreatitis hinges on various factors, notably the "systemic inflammatory response syndrome (SIRS)", organ failure, and the presence of necrotizing pancreatitis. SIRS embodies the body's reaction to inflammation, marked by symptoms like fever, rapid heart rate, and irregular white blood cell count. Organ failure often arises from this inflammatory cascade, resulting in the malfunction of multiple bodily systems. Necrotizing pancreatitis signifies tissue death within the pancreas, intensifying the gravity of the condition. Understanding these factors is crucial for prognostication and devising effective management strategies in acute pancreatitis [12-14].

During "acute pancreatitis (AP)", the chain reaction of inflammation takes the lead, stemming from pancreatic injury caused by various factors like toxins or gallstones. This injury initiates a sequence where inflammatory mediators and cytokines, such as interleukins and tumour necrosis factor, spark a systemic inflammatory response that can culminate in multiple organ failure. As the initial harm unfolds, acinar cell demise releases intracellular components termed "damage-associated molecular patterns (DAMPs)", acting as triggers for inflammation. The influx of innate immune cells like macrophages and neutrophils into the pancreas during AP unleashes proinflammatory agents that heighten the reaction, aggravating tissue damage. The NLRP3 inflammasome and the interplay between oxidative stress and proinflammatory cytokines are also pivotal in AP, further fueling the cascade of inflammatory events and contributing to its progression, often leading to severe complications [15-19].

COX-2 inhibitors constitute a distinct group of anti-inflammatory medications targeting the cyclooxygenase-2 enzyme, which is pivotal in producing pro-inflammatory prostaglandins. Unlike traditional "non-steroidal anti-inflammatory drugs (NSAIDs)", which inhibit both COX-1 and COX-2, these drugs specifically target COX-2. By doing so, they effectively diminish inflammation and alleviate pain. The primary aim behind developing these inhibitors was to minimize the gastrointestinal adverse effects associated with NSAIDs. Selective COX-2 inhibitors like celecoxib and meloxicam exhibit improved gastrointestinal tolerance while upholding their anti-inflammatory potency [20-22].

COX-2 inhibitors, targeting the COX-2 enzyme pivotal in inflammation, show promise in reducing acute pancreatitis-induced inflammation. By curtailing inflammatory mediators like IL-6 and TNF-α, they potentially dampen the overall inflammatory response. This inhibition might impede acute pancreatitis progression to severe forms marked by systemic inflammation and organ failure. Evidence suggests COX-2 inhibitors could lower severe pancreatitis incidence and mitigate associated lung injury by modulating the inflammatory response [23,24].

Current acute pancreatitis management comprises supportive care for mild cases, antibiotics for infections, ERCP for obstructions, and surgeries

for severe complications. Lifestyle changes target alcohol and weight to prevent specific types. Treating underlying conditions aids in avoiding recurrences. However, challenges persist due to unclear causes, lack of specific preventions, variable responses, and recurrent severe episodes [25-33].

"Severe acute pancreatitis (SAP)" poses a significant threat with its high mortality rates, underscoring the pressing need for innovative preventive measures. Investigations have pinpointed gut barrier failure, systemic inflammatory response, and acute lung injury as pivotal factors contributing to SAP. Promising interventions involve targeting these mechanisms, such as interrupting mesenteric lymphatic flow or enhancing rheology and oxygen delivery. Initiatives geared towards preventing SAP are pivotal not only in alleviating its burden but also in substantially enhancing patient survival rates [34,35].

Method

Research Design

A prospective single-centre randomized controlled experiment was done during the period of one year, at the Department of General Surgery in our hospital. The research protocol was approved by the Ethics Committee of Registering Clinical Trials and registered before the experiment began. Clinical investigators had strong clinical practice training and performed their tasks separately in this investigation. Participants were randomly assigned to the control or COX-2-inhibitors group in a 1:1 ratio. The patients were divided randomly into two groups, namely, Cox-2 group and Control group. The study was conducted by collecting relevant data, cytokine measurements and queries were completed and the database was created. To treat severe abdominal discomfort, patients received intramuscular injections of 50-100 mg meperidine with a minimum 4-hour interval between treatments. Patients began oral or nasogastric/nasojejunal tube feeding as soon as stomach discomfort or bowel sounds improved. Enteral nutrition emulsion Fresubin was administered by oral or nasogastric tube. If oral or tube feeding failed to meet nutritional objectives (25 kcal/kg/d) on day 5, parenteral nutrition was supplemented with intravenous fat emulsion, amino acids, and glucose (11%), using Kabiven PI. Patients with chronic obstructive jaundice or cholangitis underwent endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic papillotomy. Intravenous imipenem or meropenem was given to patients with infected necrosis or suspected necrotic pancreatitis. Patients in the COX-2 group received selective COX-2 inhibitors, parecoxib and celecoxib, sequentially at a dosage of 40 mg per day intravenous injection for 3 days, followed by 200 mg oral or tube feeding twice daily for 7 days. Control group received placebo drugs. All patients were assessed daily using APACHE-II, SIRS, and OF (1) scores for 8 days following the beginning of therapy. OF was assessed using the modified Marshall grading method. The patients self-assessed abdominal pain ratings every 4 hours for the first 3 days, ranging from 0 to 10. CRP levels were determined using Beckman Coulter's anti-CRP antibody in a scattering turbidimetric immunoassay. To measure IL-6, an antibody against it was used in an electrical chemiluminescent immunoassay. Follow-up study was done and organ failures, occurrence of severe acute pancreatitis and secondary outcomes were assessed using the scoring systems mentioned above and analyzed statistically between the groups anc conclusion was drawn.

Inclusion and exclusion criteria

Inclusion

Each patient diagnosed with AP in the emergency room was re-evaluated against the Atlanta criteria upon admission. APACHE II scores were calculated for each subject. Patients were included if they were aged 18-70, had a confirmed diagnosis of AP, had a 48-hour time interval between symptom onset and admission, had an APACHE II score of 8, and provided written informed consent.

Exclusion

Pregnancy, breastfeeding, severe chronic diseases (e.g., cardiac dysfunction, COPD, renal insufficiency, cirrhosis, inflammatory bowel diseases, malignancies), peptic ulcer, trauma-related pancreatitis, drug allergy, drug abuse, and psychosis.

Statistical analysis

The study used SPSS 27 for effective analysis. MS Excel was used for creating graphs and other calculations. the continuous data were expressed as mean±standard deviation while the discrete data were expressed as frequency and its respective percentage. Continuous variables were compared using independent-sample T or Mann-Whitney U tests. Categorical variables were analyzed using x2 or Fisher exact tests. Statistical significance was determined by a P-value of 0.05.

Result

When comparing the 55 participants who participated in the control group with those who participated in the Cox-2 group at baseline in Table 1. There were no statistically significant variations in the distribution of sexes (p=1.787), ages (p=0.353), or body mass index (p=0.458). There was no significant variance (p=0.969) in the distribution of etiologies. No statistically significant differences were seen between the groups with respect to disease severity measures such as OF scores, SIRS scores, and Apache II scores. Both the percentage of subjects with CRP levels >150 mg/L and the serum CRP levels were similar (p=0.818, p=0.835). Similarities were also found in the frequency of ERCP use (p=0.793). The Cox-2 group and the control group were quite similar at baseline.

Table 1: Characteristics of the patients at baseline

Baseline characteristics	Control (n 55)	Cox-2 group (n 55)	P-value
Sex (m/f)	30/25	35/20	1.787
Age (y, mean 6 SD)	45.82 +10.38 -	45.71+11.19 -	0.353
BMI (kg/m2 , mean 6 SD)	24.44+ 2.17 -	26.74+1.88 -	0.458
Etiology: n (%)			0.969
Biliary	30 (54.54%)	20 (36.36%)	
Alcohol	10 (18.18%)	15 (27.27%)	
Hypertriglyceridemia (.11.3 mmol/L)	10 (18.18%)	18 (32.72%)	
Other	5 (9.09%)	9 (16.36%)	
Disease severity			
Apache II scores, median (range)	10 (7–14)	10 (7–14)	1.131
OF scores, median (range)	2 (0–4)	1 (0–5)	0.652
SIRS scores	2 (3–5)	3 (2–3)	1.678
CRP in serum			
Mean 6 SD	227.96+98.57 -	233.58+94.17 -	0.818
$150 mg/L, n	53	55	0.835
ERCP, n (%)	20 (36.36%)	22 (40.00%)	0.793

The Cox-2 group (45.45%) had a substantially greater rate of Severe Acute Pancreatitis (SAP) than the control group (36.36%) (p-value 0.006). It was not significant that the control group had 9.09% mortality and the Cox-2 group 12.72% (p=0.632). Figure 1 may show both groups' Severe Acute Pancreatitis rates. The treatment's elevated SAP rate in the Cox-2 group shows a link, warranting additional study of its effects on disease severity.

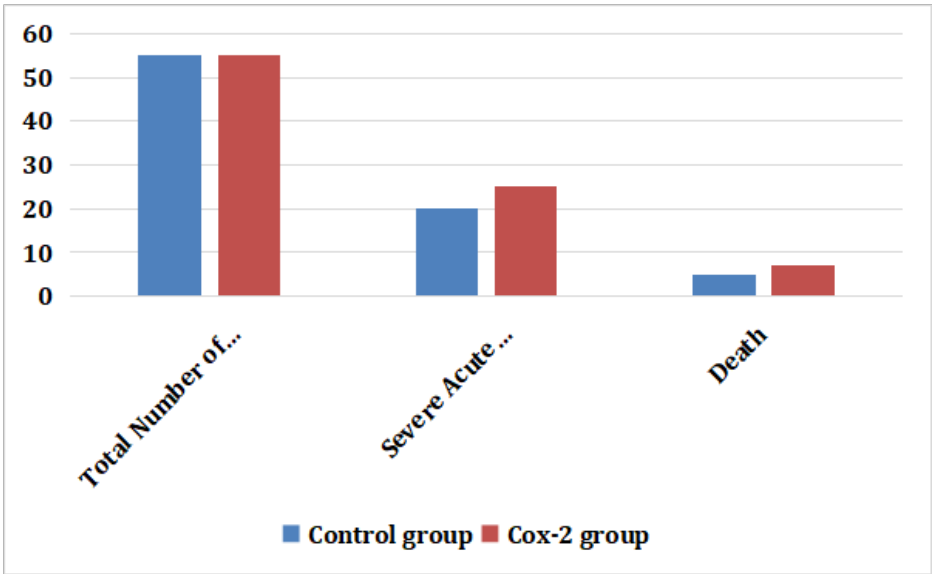

Figure 1: Occurrence of Severe Acute Pancreatitis in both the groups

Figure 2 shows that the control (n=55) and Cox-2 (n=55) groups had significantly different organ failure (OF) ratings at Day 4 and Day 8. On Day 4, the median OF score in the control group was 6, but in the Cox-2 group, it was 1 (p=0.030). By Day 8, the control group had a median OF score of 2 compared to 0 in the Cox-2 group (p=0.001). Figure 2 may show these scores, indicating that Cox-2 therapy may reduce organ failure and improve patient outcomes.

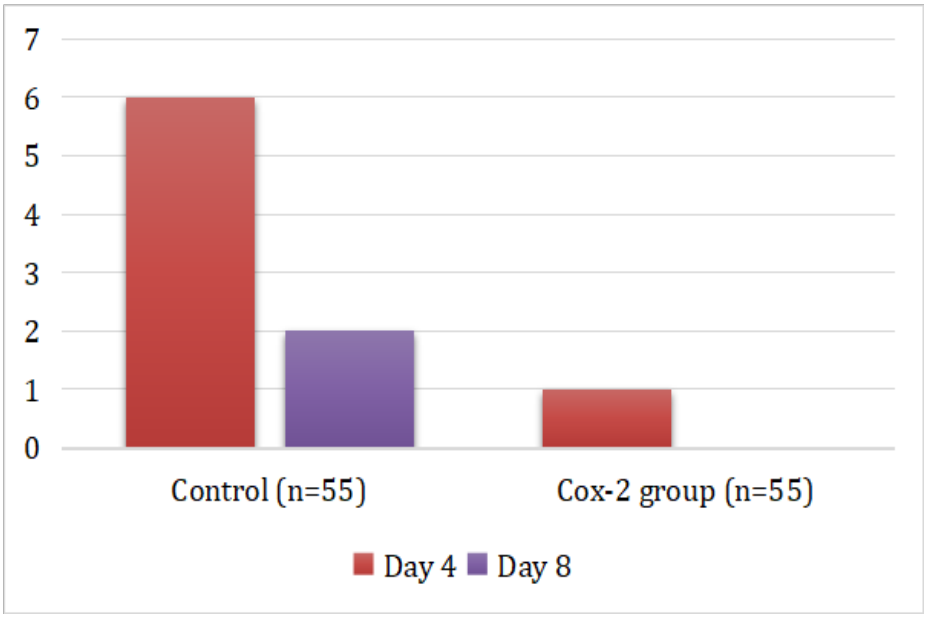

Figure 2: Scores of Organ Failure

The control and Cox-2 groups were compared on secondary outcome indicators on days 4 and 8 in Table 2. On day 4 there were 4 APACHE-II scores instead of 6, and on day 8 there were 3 instead of 4, suggesting that the illness severity may have been lowered in the Cox-2 group. With lower SIRS scores (Day 4: 1 vs. 3; Day 8: 0 vs. 1), the Cox-2 group seemed to have a more effective systemic inflammatory response. At both time periods, the Cox-2 group had significantly lower serum CRP levels, with a decreased percentage with CRP >150 mg/L. Cox-2 therapy may have a positive effect on secondary outcomes, according to these results.

Table 2: Part of secondary outcomes in both the groups

Scores	Day 4		Day 8	
	Control	COX-2 group	Control	COX-2 group
APACHE-II	6 (0–15)	4 (0–13)	4 (0–13)	3 (0–12)
SIRS score	3 (0–5)	1 (0–5)	1 (0–4)	0 (0–4)
CRP in serum				
Mean	206.38+56.37	177.22+42.70	179.34+40.37	112.59+35.58
.>_150 mg/l	44	40	40	24

Table 3 shows APACHE II and late local complications outcomes. A decreased frequency of walled-off necrosis (11 vs. 22, p=0.039) and a considerably lower incidence of late local complications (32.72% vs. 52.72%, p=0.015) were seen in the Cox-2 group. Compared to the control group, those in the Cox-2 model used meperidine injections far less often (72.72% vs. 89.09%, p=0.002). The Cox-2 group had a much lower hospital expenditure (26789.39 vs. 36281.20 VRMB, p=0.002) and a shorter hospital stay (12.89 vs. 19.40 days, p=0.16). These results provide further evidence that Cox-2 therapy for pancreatitis may improve outcomes, reduce complications, and save costs.

Table 3: Secondary Outcomes of the study

Parameters	Control	COX-2 group	P-value
Late local complications, n(%)	29 (52.72%)	18 (32.72%)	0.015
Walled off necrosis ,n	22	11	0.039
Sterile/infected, n	12/10	7/4	0.599
Drainage or necrosectomy, n	7	4	0.588
Pancreate pseudocyst, n	8	5	0.571
Drainage, n	4	3	0.592
Total fluid in the first 72 hr (mL), mean +_ SD	12879.14+_2914.32	12965.29 +_2941.40	0.595
Ringer's lactate (mL), mean +_ SD	4,329.41+_281.41	4109.41+_279.29	0.289
Colloid (mL), mean +_ SD	3785.45+_469.78	3689.30+_379.51	0.678
The type of nutritional support			0.411
Oral feeding, n	32	39	
Nasogastric tube feeding, n	20	11	
Meperidine injection, n (%)	49 (89.09%)	40 (72.72%)	0.002
Hospital staying (d), mean +_ SD	19.40+_5.61	12.89+_4.11	0.16
Hospital costs (VRMB), mean +_ SD	36281.20+_1678.59	26789.39+_851.29	0.002

Discussion

In the pursuit of addressing severe acute pancreatitis (SAP), a study by Huang et al. (2020) investigated the potential preventive impact of selective cyclooxygenase-2 (COX-2) inhibitors. 190 patients at risk for SAP were randomized into two groups: one receiving conventional treatment alone and the other treated with COX-2 inhibitors (C+COX-2-Is). Besides standard care, the C+COX-2-Is group received parecoxib intravenously (40 mg/day for 3 days) followed by oral/tube feeding celecoxib (200 mg twice daily for 7 days). The primary goal was to assess SAP occurrence. Results revealed a significant decrease in SAP incidence in the C+COX-2-Is group, 21.05% vs 39.78% in the convention group (P = 0.005). Furthermore, late local complications decreased notably in the C+COX-2-Is group,

18.95% vs 34.41% (P = 0.016). Levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were notably lower in the C+COX-2-Is group (P < 0.05). Parecoxib demonstrated faster relief of abdominal pain and reduced meperidine consumption. The study highlighted a cost reduction of RMB475 for every 1% decrease in SAP occurrence, demonstrating good cost-effectiveness. Overall, the sequential administration of parecoxib and celecoxib showed promise in halving SAP occurrence by reducing inflammatory markers, illustrating favorable cost-effectiveness [23].

In an investigation by Seo et al. (2007) on the impact of the selective Cyclooxygenase-2 (COX-2) inhibitor 4-[5-(4-Chloro-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (SC-236) in rats induced with cholecystokinin (CCK)-octapeptide-induced acute pancreatitis (AP), three groups of Wistar rats were subjected to distinct treatments. One group received normal DMSO treatment, the second group was treated with SC-236 at 4 mg/kg followed by repeated CCK octapeptide administration over five days, and the third group received DMSO treatment with a similar protocol as the SC-236 cohort. The CCK-octapeptide treatment led to induced pancreatitis in the rats. Results indicated that SC-236 administration ameliorated the severity of CCK-octapeptide-induced AP based on laboratory criteria, demonstrating reduced pancreatic weight/body weight ratio, lower levels of serum amylase and lipase, and minimal histological evidence of pancreatitis. Additionally, SC-236 treatment significantly reduced myeloperoxidase activity and increased heat shock protein (HSP)-60 and HSP72 levels while decreasing COX-2 expression in the pancreas. Moreover, SC-236 reduced proinflammatory cytokine production, inhibited NF-kappaB activation, and demonstrated a pivotal role of COX-2 in AP development, suggesting the potential of COX-2 inhibitors in preventing AP [36].

Examining articles from MEDLINE, Embase, and Cochrane, a study by Wu et al. (2020) evaluated NSAIDs' effectiveness in treating acute pancreatitis (AP) and its systemic complications. 36 studies, comprising 5 clinical trials involving 580 patients and 31 animal studies with 1623 rats or mice, were meticulously analyzed. Preclinical and clinical investigations revealed potential benefits of NSAIDs against AP-related injuries. Among the animal studies, 9 out of 14 demonstrated a significant reduction in serum amylase levels, while 6 out of 7 exhibited marked decreases in lipase levels with NSAID treatment. In all 17 experimental studies, NSAIDs notably reduced inflammation, and histopathological examinations consistently revealed improved tissue damage. Clinical evidence also supported NSAID efficacy in suppressing proinflammatory cytokines, alleviating pain, addressing systemic complications, and reducing mortality rates. Importantly, serious adverse events linked to NSAIDs were infrequent in the 5 clinical studies. This comprehensive review underscores NSAIDs, including COX-2 inhibitors, as promising treatments for ameliorating inflammation and enhancing outcomes in acute pancreatitis [37].

The scrutiny surrounding COX-2 inhibitors has centered on their safety, diverging from traditional NSAIDs due to intended reductions in gastrointestinal complications. Nevertheless, research has flagged concerns about potential cardiovascular risks linked to these inhibitors. Evidence points to increased susceptibility to cardiovascular events like hypertension, heart failure, and edema in users. Moreover, gastrointestinal adverse effects, notably abdominal pain, have surfaced in association with these drugs. Prescribing COX-2 inhibitors demands a careful balance, necessitating a thorough consideration of their prospective risks and benefits for individual patients [38-42].

“Chronic pancreatitis (CP)” poses a persistent challenge, marked by enduring inflammation and fibrosis. Exploring aspirin's potential in this realm, a study by Xu et al. (2022) investigated its therapeutic impact on CP in mice. Using a murine CP model induced by L-arginine, the research administered aspirin (100mg/kg/d) post-CP induction. Analysis at various intervals revealed notable reductions in inflammatory enzyme COX-2 expression following aspirin treatment. In these models, aspirin showcased promising outcomes by mitigating pancreatic injury, suppressing inflammatory markers (like amylase, CK-19,

F4/80, CD3, MCP-1, IL-6), and curbing fibrosis indicators (COL1A1, MMP-1, TIMP-1). Validation in a caerulein-induced CP model further reinforced aspirin's therapeutic potential. Aspirin demonstrated efficacy in lessening pancreatic inflammation and fibrosis [43].

COX-2 inhibitors, notably celecoxib, have emerged as potential preventatives for pancreatitis, credited for their anti-inflammatory properties observed in experimental pancreatitis models. These inhibitors showcased a capacity to diminish pancreatic inflammation and injury in select studies. However, the extent of their impact in preventing pancreatitis remains elusive, necessitating further exploration. Future research avenues might delve into unraveling the precise mechanisms underlying the protective influence of COX-2 inhibitors, determining optimal dosage schedules, timing of administration, and potential interactions with concurrent medications used in pancreatitis treatment [44].

COX-2 inhibitors offer promising advantages. These inhibitors exhibit a capacity to curtail the systemic release of pivotal inflammatory cytokines, notably IL-6 and IL-10, crucial in the onset of severe acute pancreatitis (SAP). COX-2 inhibitors showcase a potential shield for the pancreas, potentially reducing direct injury caused by factors like taurocholate. Clinical trials unveiled a significant decrease in SAP occurrence and subsequent late local complications through the sequential administration of parecoxib followed by a selective COX-2 inhibitor, celecoxib [45-49].

Conclusion

In conclusion, the successive administration of COX-2 inhibitors (parecoxib and celecoxib) in patients who were anticipated to have SAP resulted in a decrease of almost half of the incidence of SAP. This was accomplished by lowering blood levels of TNF-a and IL-6. This treatment protocol demonstrated favourable cost-effectiveness and effectively alleviated abdominal discomfort, resulting in reduced intake of meperidine.

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