Original Research Article

A novel treatment protocol in severe acute pancreatitis: the first double blinded comparative trial to assess efficiency of omega 3 fatty acid infusion

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ABSTRACT

Background: For decades, the treatment of acute pancreatitis (AP) has been largely supportive. However, a therapeutic window for intervention using immune modulators exists between the onset of clinical symptoms and peak pro-inflammatory cytokine expression. Soybean oil derived ω-3 PUFA is shown to inhibit the formation of ω-6 PUFA derived pro-inflammatory eicosanoids and suppresses pro-inflammatory activity of nuclear transcription factors (NF-κβ); thus, bringing about a much-needed immune regulation, both locally and systemically. Our aim was to study the efficacy of ω-3 PUFA infusion in severe AP (SAP) and set a new treatment protocol.
Methods: This, first of its kind, doubled blinded randomised control trial was undertaken to assess the efficacy of early ω-3 PUFA supplementation in patients with predicted SAP by using serum amylase, serum lipase and C-reactive protein (CRP) with BISAP and Marshal scoring systems as markers for clinical outcome. 60 such patients were randomised into two groups: 30 were given ω-3 PUFA infusion and 30 were given a placebo. Chi square test and unpaired t test were used for comparison.
Results: ω-3 PUFA infusion was found to be highly significant (p<0.05) in bringing about clinical improvement, reduced progression of SAP, reduced hospital stay and prompt reversal of organ dysfunction and SIRS.
Conclusions: ω-3 PUFA infusion is the future for the treatment of patients with SAP. This drug is cheap and easily available, has no known side effects, reduces the morbidity and mortality, reduces the duration of hospital stay; thus, resulting in overall reduced medical expenditure.

Keywords: Acute pancreatitis, Severe acute pancreatitis, Celepid, ω-3 PUFA infusion, ω-3 fatty acid

INTRODUCTION

AP is a common immunoinflammatory disorder due to premature activation and retention of potent proteolytic enzymes causing autodigestion of pancreatic acini.[1] Unregulated release of pro-inflammatory cytokines is shown to escalate the localized pancreatic inflammation into a generalized systemic inflammatory response syndrome (SIRS), wherein nearly 20% of AP patients evolve into SAP with simultaneous increase in mortality rate to 20% due to significantly higher incidence of pulmonary, renal and cardiovascular complications.[2-5] This lengthens the hospital stay and increases mortality rates unless early targeted therapy is instituted.[6,7] The degree of this unregulated cytokine increase correlates with the severity of the inflammatory response; therefore, serum amylase, serum lipase, IL-6, IL-8, IL-10, TNF-α and CRP are used as markers for the same.[8-12] Hence, attempts to suppress this hyper inflammatory response, prevention of infection and reestablishment of tissue and organ homeostasis should be the main target areas in the management protocol.

Recent evidence suggested that fish oil or soyabean oil derived ω-3 PUFA, when administered along with adequate nutritional support, was beneficial in dampening inflammation by inhibiting the formation of ω-6 PUFA derived-pro-inflammatory eicosanoids (e.g. PGE2 and LTB4) and suppressing the activity of pro-inflammatory nuclear transcription factors NF-κβ; thus bringing about a much needed regulation in the amount of inflammatory cytokines released both locally and systemically.[13-18] This reduced the progression of SAP and end organ systemic complications, lower the rates of infective complications, shortened hospital and ICU stay; thereby increasing the overall quality of life.[19]

This, first of its kind, doubled blinded randomised control trial, was planned to assess the effect of early ω-3 PUFA supplementation on clinical outcomes of SAP by using serum amylase, serum lipase and CRP with BISAP and Marshal scoring systems as markers for clinical outcome.

METHODS

This study was conducted in department of general surgery of Jagadguru Jayadeva Murugharajendra medical college in Chigateri district general hospital and Bapuji hospital, Davangere over a period of 24 months from October 2018 to September 2020 as per the ICH good clinical practice (GCP) standards. Approval was obtained from the institutional ethics committee.

Study design

This single centre, prospective, randomized controlled study was conducted to evaluate and compare the efficacy and immunomodulatory effects of ω-3 PUFA infusion (CELEPID® MCT LCT 20% 250 ml w/v Otsuka pharmaceutical India private limited) in 60 consecutive patients with predicted SAP, by using serum amylase, serum lipase and CRP with BISAP and Marshal scoring systems as markers for clinical outcome. 60 cases were randomized into two groups: study (SG) and control (CG) by computer-generated double-blinded closed envelop method and reported clinical outcomes were documented.

Inclusion criteria

Patients aged 18-70 years, from both sex, with a diagnosis of AP that was established on the basis of Atlanta guideline citeria, that is, any 2 out of 3 (clinical features suggestive of AP; serum amylase and lipase levels raised more than thrice its normal upper limit and USG or CT showing features suggestive of AP), patients with onset of pain abdomen within 24 hours of admission to hospital were included in the study. Also, patients predicted to have SAP wee those with features of SIRS defined by the presence of 2 or more of the following criteria: oral temp >100.4ºF (38ºC) or <96.8ºF (36ºC); pulse >90 beats per minute; respiratory rate >20 cpm and WBC count >12,000 cells/cumm or <4000 cells/cumm were also included in the study.

Exclusion criteria

Patients with known allergy to medium and long chain triglycerides, omega 3 and 6 fatty acids and soya bean oil; patients with immunodeficiency, that is, HIV reactive or CD4 count <200 cells/cumm, patients with primary hypertriglyceridemia, severe cardiac disease like arrhythmias (atrial flutter/fibrillation, ventricular fibrillation), patients with known renal compromise (serum creatinine >2.0 mg/dl), with known hepatic compromise (total bilirubin >1.5 times the normal upper limit), patients who received parenteral nutrition in the last 2 weeks and patients with psychiatric disorders were excluded from the study.

Study protocol

At the initial screening visit, the diagnosis of AP and presence of SIRS was confirmed by clinical, biochemical and radiological investigations. After verifying the absence of any exclusion criteria, 60 such SAP patients were inducted into the trial and by using computer-based randomization method were randomly allocated into one of the two treatment arms. The SG received a single dose of ω-3 (CELEPID® MCT LCT 20% 250 ml) infusion at a rate of 60 ml/hr over 4-5 hours whereas the CG didn't receive this infusion but received a placebo (normal saline) at the same rate as the study group. The symptomatic treatment was common: fluid therapy 25-35 ml/kg/day, analgesia (according to WHO pain pyramid started with injection paracetamol and escalated to injection tramadol/injection morphine) and supportive therapy in the form of proton pump inhibitors (PPI's) and antiemetics as per standard treatment protocols. No antibiotics were given in either group unless infection was proved by haematology or clinical signs/symptoms (Dutch pancreatitis study group 2011). Serum amylase, serum lipase and CRP levels were sent and BISAP and Marshall scores were assessed on admission and again after 48 hours post-infusion. Patients having a BISAP score ≥3 or a Marshall score ≥ 2 on day 0 as well as day 3 or a persistently elevated CRP >150 mg/ml on day 3 were diagnosed to have persistent organ failure, thereby confirming the progression of SAP.

Clinical parameters

Progression of SAP, mean hospital stay, number of days on the ventilator (if any) were observed in the two groups and compared.

Laboratory parameters

Serum amylase levels done on admission (day 0) and after 48 hours post-infusion (day 3). Serum lipase levels done on admission (day 0) and after 48 hours post-

infusion (day 3). Serum CRP levels done on admission (day 0) and after 48 hours post-infusion (day 3).

BISAP score

Evaluation done on admission (day 0) after 48 hours post-infusion (day 3).

Marshall's score

Evaluation done on admission (day 0) and after 48 hours post-infusion (day 3).

Table 1: BISAP scoring system.

Parameters	Score 0	Score 1
Blood urea nitrogen (BUN) (mg/dl)	<25	>25
Impaired mental status	Absent	Present
SIRS	Absent	Present
Age (in years)	<60	>60
Pleural effusion	Absent	Present

Table 2: Marshall scoring system.

Organ system	Scores				
	0	1	2	3	4
Respiratory (PaO2/FIO2)	>400	301-400	201-300	101-200	≤101
Renal (serum creatinine, mg/Dl)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg)	>90	<90 responsive to fluid therapy	<90 non-responsive to fluid therapy	<90 Ph <7.3	<90 Ph <7.2

Statistical analysis

Statistical analysis was performed by using SPSS computer software v.21.0. Chi square test and unpaired t test were used for comparison. $P<0.05$ was taken as level of statistical significance.

RESULTS

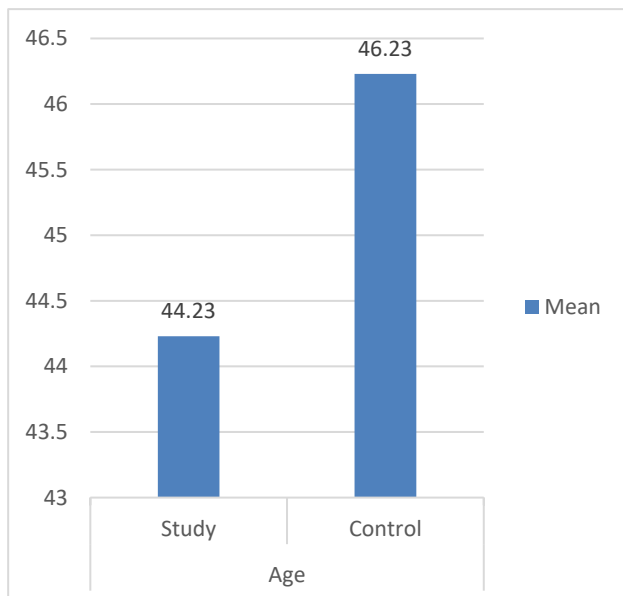The two groups were comparable in terms of demographics, etiology and habits ($p>0.05$).

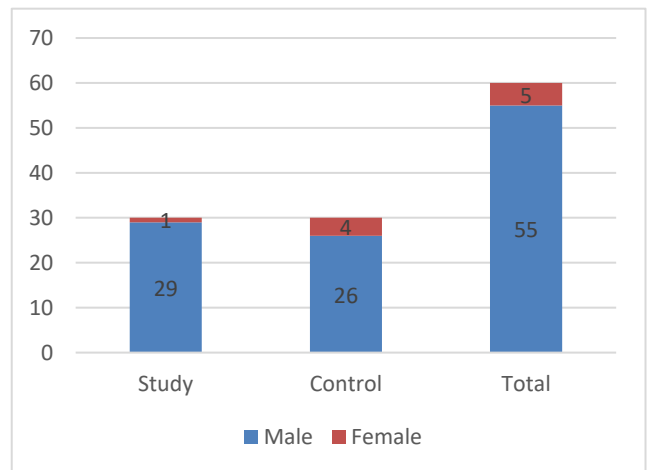**Figure 1: Mean age distribution.**
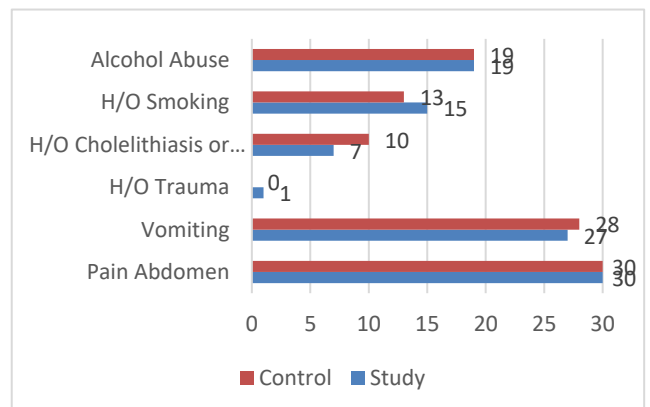

Figure 2: Sex distribution.

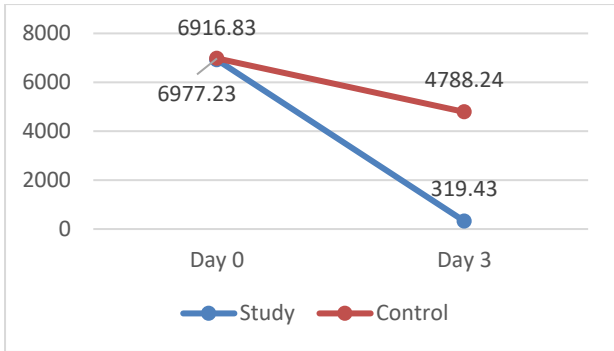**Figure 3: Comparison of history and symptoms between both the groups.**

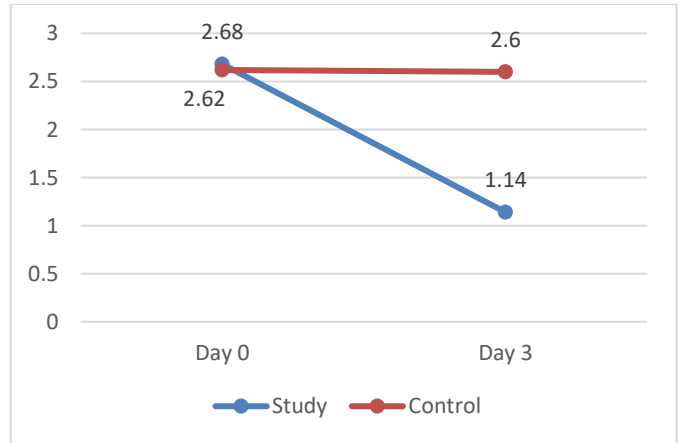**Figure 4: Comparison of serum amylase levels between both groups.**

Figure 5: Comparison of serum lipase levels between both groups.

Figure 6: Comparison of CRP levels between both groups.

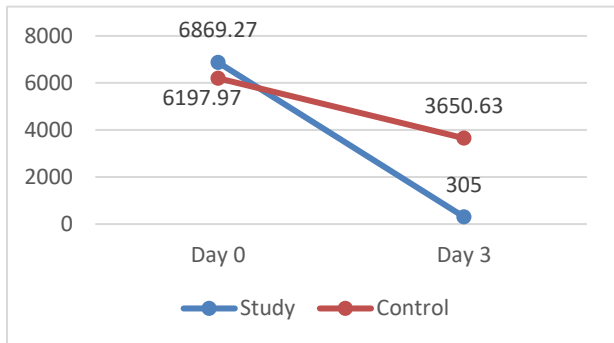**Figure 7: Comparison of BISAP scores between both groups.**

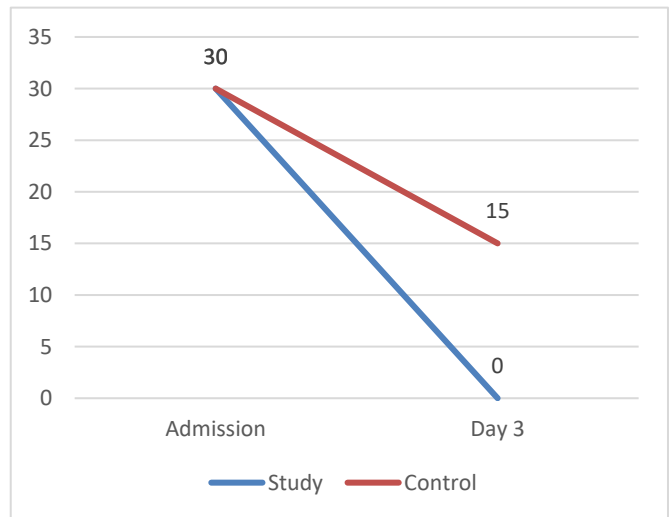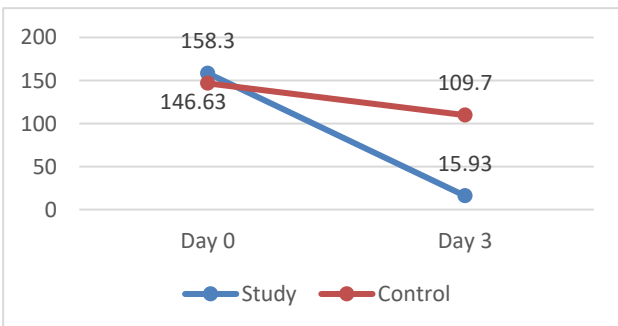**Figure 8: Comparison of Marshall scores between both groups.**
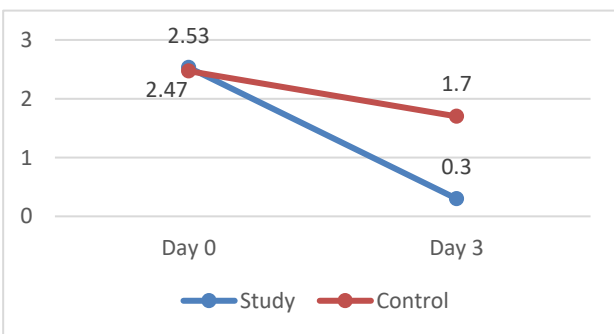

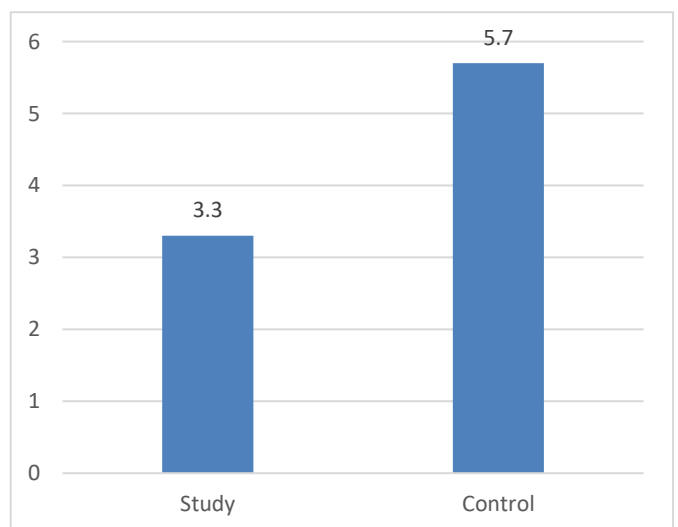**Figure 9: Comparison of persistence/progression of SAP between both groups.**

Figure 10: Comparison of mean duration of hospital stay of both groups.

Table 3: Comparison of serum amylase levels between both groups.

Sr. amylase	Group	Number	Mean (IU/l)	Standard deviation	P value	
Day 0	Study	30	6916.83	±2642.64	0.33	Non-significant
	Control	30	6977.23	±2128.11		
Day 3	Study	30	319.43	±541.44	0.00	Significant
	Group	30	4788.24	±2228.79		

Table 4: Comparison of serum lipase levels between both groups.

Sr. lipase	Group	Number	Mean (IU/l)	Standard deviation	P value	
Day 0	Study	30	6869.27	±2847.08	0.33	Non-significant
	Control	30	6197.97	±2516.56		
Day 3	Study	30	305	±578.69	0.00	Significant
	Group	30	3650.63	±2056.51		

Table 5: Comparison of serum CRP levels between both groups.

Sr. CRP	Group	Number	Mean (IU/l)	Standard deviation	P value	
Day 0	Study	30	158.3	±56.66	0.42	Non-significant
	Control	30	146.63	±53.29		
Day 3	Study	30	15.93	±4.62	0.00	Significant
	Control	30	109.7	±58.83		

Table 6: Comparison of BISAP score between both groups.

BISAP	Group	Mean	Standard deviation	P value	
Day 0	Study	2.53	±0.92	0.62	Non-significant
	Control	2.47	±0.51		
Day 3	Study	0.3	±0.6	0.00	Significant
	Control	1.7	±0.92		

Table 7: Comparison of Marshall score between both groups.

BISAP	Group	Mean	Standard deviation	P value	
Day 0	Study	2.68	±0.621	0.615	Non-significant
	Control	2.62	±0.567		
Day 3	Study	1.14	±0.495	0.00	Significant
	Control	2.64	±0.563		

Age (SG: mean age 44.23 years and CG: mean age 46.23 years) (p=0.58) not significant (Figure 1).

Sex (SG: 29 male 1 female and CG: 26 male 4 female) (p= 0.35) not significant (Figure 2).

All 60 patients presented with severe, continuous pain felt over the upper abdomen with characteristic radiation to the upper back. 55 patients c/o nausea with vomiting (SG: 27 and CG: 28) (p=1.00) not significant. One case in SG had blunt trauma associated pancreatitis which was statistically not significant (p=1.00). 17 patients presented with gall stone induced pancreatitis (SG: 7 and CG: 10) (p=0.58) not significant. 28 patients had h/o smoking tobacco (SG: 15 and CG: 13) (p=0.80) not significant. 38 patients presented with alcohol induced pancreatitis (SG: 19 and CG: 19) (p=1) not significant (Figure 3).

On admission, mean amylase levels in SG was 6916.83 IU/l and in CG was 6277.23 IU/l (p=0.33) not significant. 48 hours post infusion, the mean amylase levels in SG was 319.43 IU/l and in CG was 4788.24 IU/l (p=0) significant reduction (+) (Table 3) (Figure 4).

On admission, mean lipase levels in SG was 6869.27 IU/l and in CG was 6197.97 IU/l (p=0.33) not significant. 48 hours post infusion, the mean lipase levels in SG was 305 IU/l and in CG was 3650.63 IU/l (p=0) significant reduction (+) (Table 4) (Figure 5).

On admission, mean CRP levels in SG was 158.3 mg/l and in CG was 146.63 mg/l (p=0.42) not significant. 48 hours post infusion, the mean CRP levels in SG was 15.93 mg/l and in CG was 109.60 mg/l (p=0) significant reduction (+) (Table 5) (Figure 6).

On admission, mean BISAP score in SG was 2.53 and in CG was 2.47 (p=0.62) not significant. 48 hours post infusion, the mean BISAP score in SG was 0.3 and in CG was 1.7 (p=0) significant reduction (+) (Table 6) (Figure 7).

On admission, mean Marshall score in SG was 2.68 and in CG was 2.62 (p=0.615) not significant. 48 hours post infusion, the mean Marshall score in SG was 1.14 and in CG was 2.60 (p=0) significant reduction (+) (Table 7) (Figure 8).

None of the patients in SG progressed to severe transient/persistent AP but 15 out of the 30 patients in CG showed a progressive course (p=0.002) highly significant (Figure 9).

One patient in SG was on mechanical ventilation; she recovered well and was extubated on 3rd day. Similarly, one patient in CG was on mechanical ventilation; she recovered well and was extubated on 4th day (p=0.98) not significant.

Mean hospital stay in SG was 3.3 days and in CG was 5.7 days (p=0) significant reduction (+) (Figure 10).

DISCUSSION

At present, the treatment AP and SAP was largely supportive. However, a therapeutic window for intervention with immune-modulators existed between the onset of clinical symptoms and peak pro-inflammatory cytokine expression. Excessive acinar cell injury with unregulated release of pro-inflammatory cytokines was shown to escalate the localized pancreatic inflammation into a generalized SIRS with significantly higher incidence of pulmonary, renal and cardiovascular complications unless early targeted therapy was instituted.[2-7] The degree of this unregulated cytokine increase correlated with the severity of the inflammatory response leading to the use of serum amylase, serum lipase, IL-6, IL-8, IL-10, TNF-α and CRP as markers to assess the same, which had been validated by several studies.[8-12]

ω-3 and ω-6 PUFA were the precursors of the lipid mediators and played an important role in regulation of inflammation. ω-6 PUFA (e.g. arachidonic acid) promoted inflammation whereas ω-3 PUFA (e.g. eicosapentanoic acid and docosahexanoic acid) have anti-inflammatory properties by inhibiting the formation of ω-6 PUFA-derived pro-inflammatory eicosanoids (e.g. PGE2 and LTB4) and suppressing the activity of nuclear transcription factors (NF-κβ) both locally and systemically as demonstrated in several trials.[13-18] This regulation was expected to lower the rates of infective complications, shorten the hospital and ICU stay, lower progression SAP and increase the overall quality of life.[19]

In our study consisting of 60 SAP patients; both groups were comparable in terms of demographics, etiology, habits and symptomatology (p>0.05). A single dose of ω-3 PUFA infusion (in SG) bought about a statistically significant reduction (p<0.05) in the serum amylase, serum lipase, CRP levels, BISAP and Marshall scores. It also demonstrated a highly significant reduction in the persistence/progression of SAP as similarly demonstrated in several trials; signifying the ability of ω-3 PUFA infusion to regulate the amount of pro-inflammatory cytokines released both locally and systemically and bring a stop to the persistence and progression of organ dysfunction.[20-24] This allowed for early enteral nutrition, thus reducing the incidence of conversion of sterile necrosis into infected one; reduction in duration of hospital/ICU stay and reduction in overall morbidity and DALY.

On 6 and 12 weekly follow up, patients in SG had no complaints or relapses in terms of symptomatology.

Limitations

This study was a small, population-based study from a single institution, from among patients diagnosed with predicted SAP admitted during a brief time-frame. Larger, rigorously designed, multi-institutional prospective studies with longer time frames are needed to conform validity and accuracy my results and analysed for further complications. Paediatric were not included in this study. Although several meta-analyses have been recently conducted in an effort to clarify whether the administration of ω-3 FA improved outcomes in patients with AP, definitive conclusions and detailed mechanism of action are lacking. Therefore, perspectives on the use of ω-3 FA treatment in critically ill patients remained conflicting.

CONCLUSION

In conclusion, the present study demonstrates that a single 250 ml infusion of Celepid® MCT LCT 20% brings about highly significant reduction of clinical and laboratory parameters of SAP. This drug is cheap and easily available, has no known side effects, reduces the morbidity, mortality and the duration of hospital stay and thus, results in overall reduced medical expenditure. Therefore, by bring about the much-needed regulation in the amount of pro-inflammatory cytokines released both locally and systemically, ω-3 PUFA infusion should be made a vital part of the management protocols for the treatment of acute pancreatitis.

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