

Original Research Article

A novel treatment protocol in acute pancreatitis: the first double blinded comparative trial of omega 3 fatty acid infusion versus octreotide

H. G. M. Rudraiah, Siddharth Vijay Kalke*, Aniruddha Desai

Department of General Surgery, JJM Medical College and Bapuji Hospital Davangere, Karnataka, India

Received: 02 October 2018

Accepted: 30 October 2018

***Correspondence:**

Dr. Siddharth Vijay Kalke,

E-mail: dr.siddharthkalke@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Over decades the treatment of acute pancreatitis remains debatable with no common consensus on treatment guidelines, with some workers using octreotide infusion and some workers only relying on fluid therapy and symptomatic management. This is the first of its kind double blinded comparative trial between omega 3 fatty acid infusion versus octreotide infusion and its response in cases of acute pancreatitis.: Our aim is to study the efficacy of omega 3 fatty acid infusion and set a new treatment protocol in cases of acute pancreatitis with the use of omega 3 fatty acid infusion in all admitted cases of acute pancreatitis unless otherwise contraindicated.

Methods: This is the first study where a doubled blinded randomised control trial was undertaken in proven cases of acute pancreatitis and patients were given omega 3 fatty acid infusion and octreotide infusion and the observations were documented and followed upon. 100 cases of proven acute pancreatitis were randomised with double blinded closed envelop method. 50 cases were given omega 3 fatty acid infusion and other 50 were given octreotide infusion and the clinical response, symptomatic improvement was assessed and compared using BISAP and Marshal scoring systems and lipase levels. Chi Square test was used along with unpaired t test and p value was obtained in both groups.

Results: Omega 3 fatty acid infusion was found to be highly significant as compared to octreotide in cases of acute pancreatitis in terms of clinical improvement, reduced hospital stay, reversal of organ dysfunction and SIRS.

Conclusions: Omega 3 fatty acid infusion is the future in cases of acute pancreatitis which is cheap and easily available with no side effects and reduces the morbidity and mortality in acute pancreatitis with reduced hospital stay in turn resulting in overall reduced medical expenditure.

Keywords: Acute pancreatitis, Celepid, Octreotide, Omega 3 fatty acid infusion, ω -3 FA

INTRODUCTION

Worldwide, over the last decade, yearly incidence of pancreatitis and related hospitalizations have increased. Acute pancreatitis is the most common cause of GI related hospitalizations in the world, with more than 274,000 hospitalizations in 2012.¹ The yearly incidence of AP in the United States is approximately 70-80 new cases per 100,000 population and has increased over the

last decade.² True incidence and prevalence of pancreatitis in India is unknown since, it being difficult to establish an accurate diagnosis, a number of cases are misdiagnosed or are not recorded or reported. Nevertheless, in 2004, a high prevalence of chronic pancreatitis in Southern India (114-200/100,000 population) was registered in a study of chronic pancreatitis in the Asia-Pacific region.³ 20% of acute pancreatitis evolve into severe acute pancreatitis at a

given point of time in the world resulting in an average mortality of 20%.⁴ Aggravated acinar cell injury causing heightened immune response, resulting in pancreatic necrosis and generation of free radicals causing; SIRS and distant organ damage resulting in MODS.⁵ Hence, attempts to enhance immune function, suppress the hyper inflammatory responses and re-establish tissue and organ homeostasis in AP patients have been made in clinical practice.⁶ Accumulating evidence has suggested that omega-3 fatty acids (ω -3 FA) can alter cytokine production, modulate inflammatory and immunological response and thus be expected to lower the rates of infectious complications, shorten the hospital stay in the intensive care unit (ICU) or on regular medical wards as well.^{7,8} Anti-inflammatory and immune-modulatory effects of ω -3 FA may provide an important therapeutic option for the patients with AP. Aim of this double blinded randomised controlled trial first of its kind it to prove that omega 3 fatty acid infusion in acute pancreatitis have magical response which is highly significant as compared to other treatment modalities like octreotide infusion. Omega 3 fatty acid infusion is the future in cases of acute pancreatitis and can reduce overall mortality and morbidity.

METHODS

This study was conducted over a period of 12 months in a tertiary care hospital in Davangere as per the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) standards. This study was a single centre, open-label, randomized, controlled, comparative phase IV study to evaluate and compare the efficacy and safety of omega 3 fatty acid infusion (Celepid MCT LCT W/V Otsuka pharmaceutical India Private Limited) in cases of acute pancreatitis. 100 cases of proven acute pancreatitis randomized in two groups Group 1 study group (Celepid MCT LCT) and Group 2 control group (Octreotide) by computer generated double blind closed envelop method and reported clinical outcomes were documented.

Inclusion criteria

1. Age- 18 to 70 years of either sex
2. Atlanta guidelines criteria- Any 2 out of 3.
 - a. Systolic BP < 90MMHG
 - b. Serum. Ca- <7.5mg/dl
 - c. Usg/CT showing acute pancreatitis
3. Serum Amylase and Lipase >3 times the normal.
4. SIRS criteria (Systemic Inflammatory Response Syndrome)
 - a. Temp >100.4
 - b. Heart rate- >90
 - c. Respiratory rate >20
 - d. WBC >12000 or <4000

Exclusion criteria

- Immunodeficiency- HIV reactive

- Primary Hypertriglyceridemia
- Severe Cardiac disease like acute myocardial infarction, congestive cardiac failure.
- Serum Creatinine- >2.0mg/dl with unavailable dialysis facility.
- Received TPN in last 2weeks.

Study protocol

During initial screening all patients with proven acute pancreatitis by blood investigations like serum amylase and serum lipase and or USG/CT were randomly allocated in two groups celepid or octreotide by computer generated double envelop method. Patient in celepid group received inj celepid MCT-LCT infusion 60ml/hr over 4-5hours (250ml infusion) single dose on admission with 150ml/hr IV fluid, pain relief with paracetamol/ Tramadol and H2 receptor antagonist and Proton pump inhibitors. Patients in octreotide group received inj octreotide 100mcg iv 8th hourly for 5 days with 150ml/hr IV fluid, pain relief with paracetamol/Tramadol and H2 receptor antagonist and Proton pump inhibitors. No antibiotics were given in either group unless infection was proved by hematology (Dutch pancreatitis study group 2011). Comparison was done on the basis of biochemical values (serum lipase), clinical scoring system in pancreatitis (BISAP score), organ dysfunction (MARSHALL score) and hospital stay and overall costs associated.

Comparison

Lipase levels on admission and on day 3 in both groups.

BISAP scoring system-

- Bun >25mg/dl (1 POINT)
- Gcs<15 (1 POINT)
- SIRS (1 POINT)
- >60 years (1 POINT)
- Pleural effusion (1 POINT)

Evaluation done-

- On admission.
- On day 3

MARSHALL scoring systems-Persistent or transient organ failure (Table 1).

RESULTS

The two groups were comparable in terms of age (celepid mean age group-40.96 yrs and octreotide mean age group 45.90 yrs) (p value-0.108) not significant (Figure 1), sex wise 49 male patients and 1 female patient in celepid group and 46 male and 4 female patients in octreotide group (p value- 0.169) not significant (Figure 2), all 100 cases had pain abdomen on admission with 43 patients in

celepid group having vomiting and 45 patients in octreotide group having vomiting (p value- 0.538) non significant. 3 cases in celepid group had blunt trauma associated pancreatitis and 1 case in octreotide group had traumatic pancreatitis (p value-0.617) non significant, 7 patients in celepid group had gall stone induced pancreatitis and 10 cases in octreotide group had gall stone induced pancreatitis (p value- 0.425) non

significant, 25 patients were smokers in celepid group and 21 were smokers in octreotide group (p value-0.422) non significant, 37 patients were alcoholic in celepid group and 34 patients were alcoholic in octreotide group (p value- 0.66) non significant (Figure 3). The two groups were comparable in terms of demographics, etiology, habits. 1 case was on mechanical ventilation in celepid group and 1 in octreotide group.

Table 1: MARSHALL score parameters and calculation.

Organ system	Score				
	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	<90	<90	<90

(a score of 2 or more over a period of more than 48 hours for any one of the three organ systems is defined as persistent organ failure while if it is present for less than 48 hours, is known as transient organ failure and level of severity should be assessed during the disease process and hospital stay using this scoring system.)

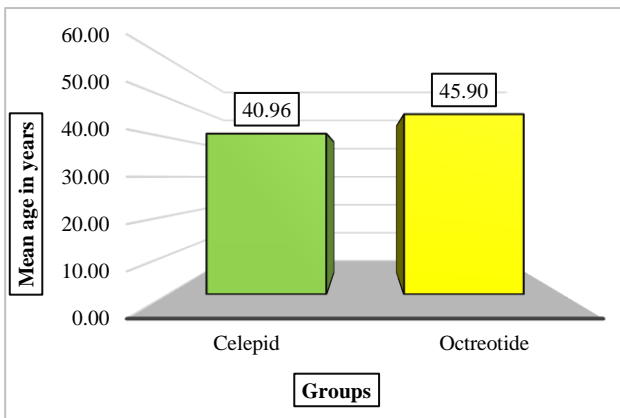


Figure 1: Age distribution of patients in both groups.

On admission mean lipase levels in celepid group was mean 6889.64 and octreotide group was mean 6508.90 (p value-0.462) not significant and day 3 lipase levels in celepid group was mean 236.04 and octreotide group was 4192.92 (p value-0.0001) highly significant (Table 2 Figure 4). On admission mean BISAP score in celepid group was 2.96 and octreotide 2.60 (p value-0.017) mildly significant and day 3 mean BISAP score was 0.32 and octreotide was 1.76 (p value-0.0001) highly significant (Table 3 Figure 5).

Mean MARSHALL score in celepid group on admission was 2.68 and octreotide 2.62 (p value-0.615) non significant. Day 3 mean MARSHALL score in celepid group was 1.14 and octreotide group 2.64 (p value-0.0001) highly significant (Table 4 Figure 6). Mean hospital stay in celepid group was 3.32 days and octreotide was 5.40 days (p value- 0.0001) highly significant (Figure 7). Patient in celepid group which was on mechanical ventilation recovered well and was extubated on 3rd day while patient in octreotide group on ventilatory support succumbed.

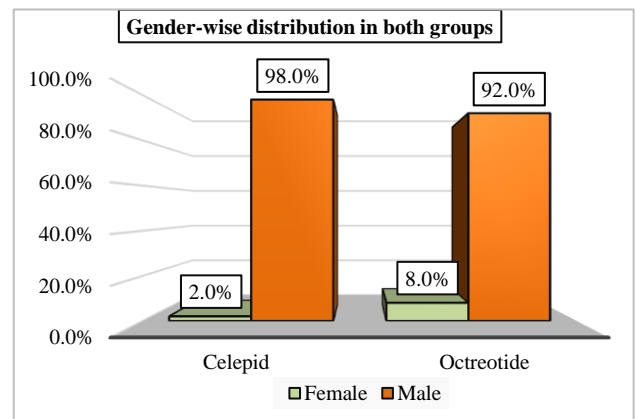


Figure 2: Gender wise distribution in both groups.

Table 2: Comparison of lipase levels in both groups.

Lipase level	N	Mean	Std. Deviation	Median	P value	
On admission	Celepid MCT LCT	50	6889.64	2671.902	7020.00	0.462 NS
	Octreotide	50	6508.90	2476.701	6918.00	
Day 3	Celepid MCT LCT	50	236.04	463.030	108.00	0.0001 S
	Octreotide	50	4192.92	2412.225	3231.00	

Table 3: Comparison of BISAP scores in both groups.

BISAP scores		N	Mean	Std. Deviation	Median	P value
On admission	Celepid MCT LCT	50	2.96	0.807	3.00	0.017 S
	Octreotide	50	2.60	0.670	3.00	
Day 3	Celepid MCT LCT	50	.32	0.653	0.00	0.0001 S
	Octreotide	50	1.76	0.847	2.00	

Table 4: Comparison of MARSHALL scores and hospital stay in both groups.

		N	Mean	Std. Deviation	Median	P value
MARSHAL score						
On admission	Celepid MCT LCT	50	2.68	0.621	3.00	0.615 NS
	Octreotide	50	2.62	0.567	3.00	
Day 3	Celepid MCT LCT	50	1.14	0.495	1.00	0.0001 S
	Octreotide	50	2.64	0.563	3.00	
Group						
Duration of stay in hospital in days	Celepid MCT LCT	50	3.32	0.978	3.00	0.0001 S
	Octreotide	50	5.40	1.629	5.00	

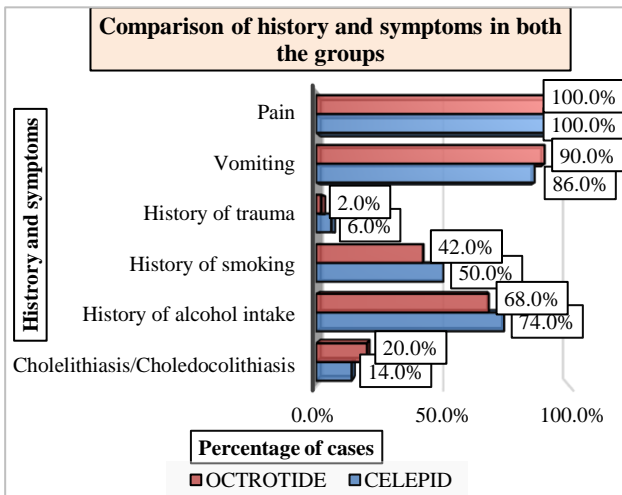


Figure 3: Etiology and risk factors in both groups.

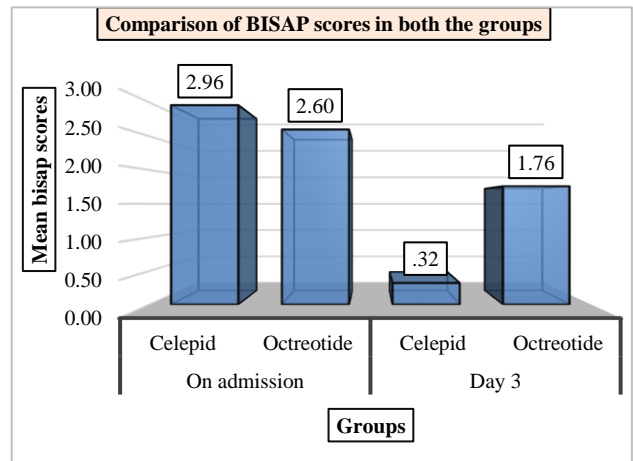


Figure 5: Comparison of BISAP scores in both groups.

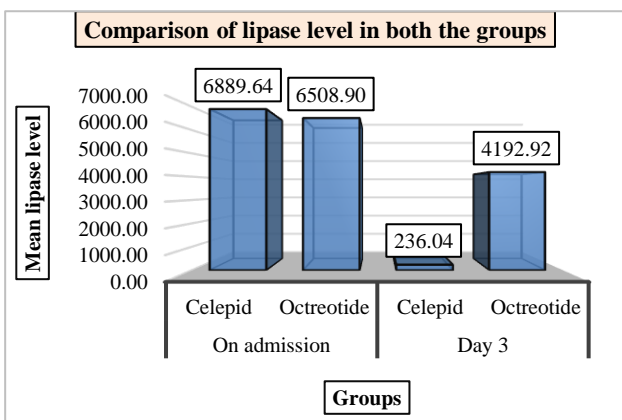


Figure 4: Comparison of lipase levels in both groups.

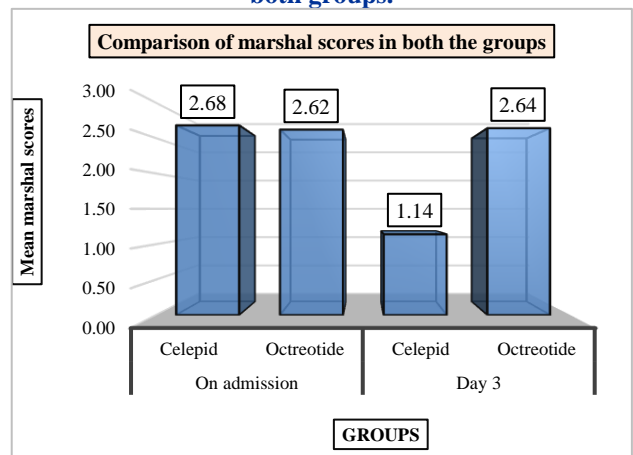


Figure 6: Comparison of MARSHALL scores in both groups.

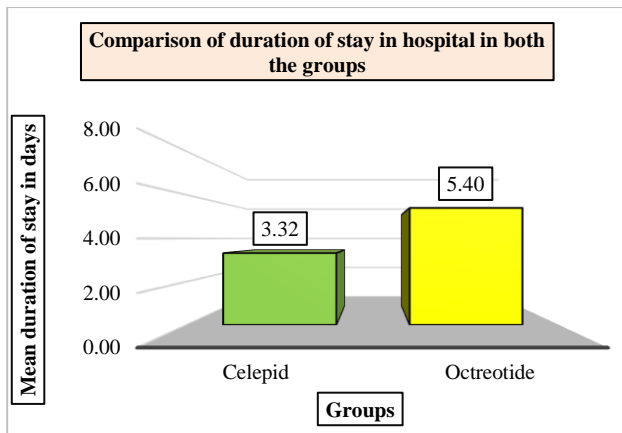


Figure 7: Comparison of hospital stay in both groups.

DISCUSSION

As per statistical analysis the use of omega 3 fatty acid turned out to be highly significant in terms of cases of acute pancreatitis where a dramatic reduction in lipase levels was noted with a single 250ml infusion of Celepid MCT LCT 20% and reduction in the overall mortality and morbidity by reduced BISAP scores. Celepid stopped the progression of organ dysfunction and mostly reversed it which was proved by reduction in the MARSHALL scores. Overall celepid reduces the early conversion of cases of acute pancreatitis to severe acute pancreatitis and halts organ dysfunction, allows early enteral nutrition thus reducing the incidence of conversion of sterile necrosis into infected one. Our trial proves that in adverant use of antibiotics in acute pancreatitis is not justified (as proved by dutch pancreatitis study group 2011). Celepid MCT LCT overall reduces the hospital stay, ICU stay, reverses SIRS AND MODS thus reducing the no of DALY's. On 6 and 12 weekly follow up patients in celepid group had no complaints or relapses in terms of symptomatology.

The treatment of acute pancreatitis at present is largely supportive. However, a therapeutic window for intervention with modulators of inflammation exists between the onset of clinical symptoms and peak pro-inflammatory cytokine expression. Polyunsaturated fatty acids (omega-3) are the precursors of the lipid mediators and play an important role in regulation of inflammation. ω -3 FA suppresses the inflammation and improves the course of infection by reducing proinflammatory eicosanoid and cytokine production. The ability of ω -3 FA to regulate these immune processes has been well described in many experimental and clinical studies.

Fish oil derived omega-3 polyunsaturated fatty acids (ω -3 PUFA) when administered along with adequate nutritional support has been reported to have a beneficial effect on the immune response; enhancing immunity, reducing inflammatory response, altering cytokine production and hence improving outcomes in AP.

Accumulating evidence has suggested that omega-3 fatty acids (ω -3 FA) can alter cytokine production, modulate inflammatory and immunological response and thus be expected to lower the rates of infectious complications, shorten the hospital stay in the intensive care unit (ICU) or on regular medical wards as well.⁷⁻⁹ Anti-inflammatory and immunomodulatory effects of ω -3 FA may provide an important therapeutic option for the patients with AP.

CONCLUSION

Although several meta-analyses have been conducted recently in an effort to clarify whether the administration of ω -3 FA improves outcomes in patients with AP, definitive conclusions have been lacking. Therefore, perspectives on the use of ω -3 FA treatment in critically ill patients remained conflicting. This is the first of its kind comparative analysis between Octreotide which proved ineffective by multiple trials in acute pancreatitis but still remains the go to drug for many workers versus omega 3 fatty acids infusion which showed promising results in our trial. Octreotide has its own side effects and is a costly drug which needs to be given 3 times a day for 5 days. A single infusion of Celepid MCT LCT 20%w/v reduces the overall burden on the patient and hospitalisation associated costs. As omega 3 fatty acid infusion (Celepid) had no side effects noted it can be safely tagged as the go to drug therapy in acute Pancreatitis Hypersensitivity ruled out per se.

ω -3 PUFA improves the early clinical outcomes of the patients of moderate to severe AP and due consideration should be given to making IV Omega- 3 PUFA supplementation part of the standard management protocols for moderate to severe AP.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not Required

REFERENCES

1. Lee P, Stevens T. Acute Pancreatitis. Cleveland Clinic 4th Annual Gastroenterology &Hepatology Symposium, 2014.
2. Lankisch PG, Banks PA. Pancreatitis. New York: Springer; 1998.
3. Garg PK, Tondon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastroenterol Hepatol. 2004;19:998-1004.
4. Winslet M, Hall C, London NJ, Neoptolemos JP. Relation of diagnostic serum amylase levels to aetiology and severity of acute pancreatitis. Gut. 1992;33:982-6.
5. Jha RK, Ma Q, Sha H, Palikhe M. Acute pancreatitis: A literature review. Med Sci Monit. 2009;15:147-56.
6. Meier R. Enteral fish oil in acute pancreatitis. Clin Nutr. 2005;24:169-71.
7. Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, et al. Short-time infusion of

fish oil based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. *J Immunol.* 2003;171:4837-43.

8. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep.* 2004;6:461-7.
9. Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H. Immunomodulation by perioperative

administration of n-3 fatty acids. *Br J Nutr.* 2002;87:89-94.

Cite this article as: Rudraiah HGM, Kalke SV, Desai A. A novel treatment protocol in acute pancreatitis- the first double blinded comparative trial of omega 3 fatty acid infusion versus octreotide. *Int Surg J* 2018;5:4052-7.