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Role of Pentoxifylline in Severe Alcoholic Hepatitis

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ABSTRACT
AIM: *Role of Pentoxifylline is compared with placebo in the treatment of Severe Alcoholic Hepatitis.*
METHODS: *Total 20 pts with severe alcoholic hepatitis (Maddrey DF ≥ 32) were included in the study.10 patients received pentoxifylline 400mg TDS for 4wks.And 10 patients received placebo for 4 wks. Baseline characteristics of the two groups were similar. Study was conducted for 4 wks.*
RESULT: *Statistical Analysis was done using student's t test. The calculated t value found to be 25.01 at 18 df which indicates the difference between Placebo and Pentoxyfylline group is highly significant (P<0.001). Higher baseline Maddrey Discriminant Function was associated with increased mortality. But Pentoxifylline lowers the Maddrey Discriminant Function thus improves survival.*
CONCLUSION: *As compared to Placebo, Pentoxifylline reduce mortality, improved risk-benefit profile and lowers Maddrey Discriminant Function in patients with severe alcoholic hepatitis. Hence it is suggested that pentoxifylline is efficacious in treatment of severe alcoholic hepatitis.*
KEYWORDS: *Severe Alcoholic hepatitis, Pentoxifylline, Prednisolone, Maddrey discriminant function.*

INTRODUCTION

Severe alcoholic hepatitis is an acute hepatic inflammatory response syndrome, which is part of the spectrum of disease that result from alcohol induced liver injury, ranging from most asymptomatic fatty liver to cirrhosis of liver. Alcoholic hepatitis is a serious disease, with a mortality of up to 60% in the first 4 weeks of diagnosis in severe cases.(1) The syndrome of alcoholic hepatitis developes in only a minority of chronic alcohol abusers (2) with a clinical spectrum ranging from an asymptomatic histological diagnosis to a life threatening clinical illness that include jaundice, ascitis, gastrointestinal bleeding and encephalopathy. The presence of coexisting hepatitis C has been found to be associated with worse prognosis.(3) Serum level of cytokines such as tumor necrosis factor (TNF-alfa),interleukin (IL-1),IL-6 and IL-8 are elevated in acute alcoholic hepatitis.(4) Maddrey discriminant function (DF) has commonly been used in estimating mortality among patients with acute alcoholic hepatitis with an elevated DF (>32) indicating an increased likelihood of death, and conversely, a low DF suggesting a generally favorable prognosis.(5,6)

Maddrey discriminant function is calclated by a simple formula:

[4.6x(PT test-control)+S. Bilirubin in mg/dl]. Prospective studies have shown that it is useful in predicting short term prognosis especially mortality within 30 days.(7) A value more than 32

implies poor outcome with one month mortality ranging between 35%-45%.[8] Prednisolone is used widely and considered the standard treatment for severe alcoholic hepatitis with DF score>32.[9] But most of the times use of Prednisolone is not feasible due to possibility of ongoing infection and other complication of Glucocorticoids. Recently Pentoxifylline a non-specific phosphodiesterase inhibitor, with combined anti-inflammatory and antifibrogenic properties found to be effective in patients with alcoholic hepatitis with DF>32.[10,11] Pentoxifylline (PTX) has been reported to be effective in inhibiting tumor necrosis factor (TNF-alfa) production by mononuclear cells.[12,13] The beneficial effects are believed to occur through various mechanism such as inhibition of phosphodiesterases, increased cAMP levels and down regulation of TNF-alfa,IL-1,IL-6,transforming growth factor beta (TGF-beta),interferon gamma ,stellate cell activation and procollagen-1 mRNA expression. [14] Basing on the above concept the present study has been designed to assess the efficacy of Pentoxifylline in treatment of alcoholic hepatitis with Maddrey Discriminant Function ≥32 .

MATERIALS AND METHODS

20 chronic alcoholic patients having maddrey DF 32 or more than 32 were included in the study. Study was conducted in dept of Gastroenterology Apollo Hospital Bhubaneswar. The patients were initially examined clinically, evaluated and were included for the study. All the patients underwent investigations like LFT,PT, Complete hemogram, RBS, urea. Patients with infection, Sepsis or spontaneous bacterial peritonitis, gastrointenstinal bleeding, hepatorenal syndrome, acute pancreatitis or any other severe associated disease malignancy, Uncontrolled diabetes, Heart failure, Pulmonary disease at the time of starting of the study were excluded from the study. All of the patients were not a candidate for steroid therapy either due to sepsis or other conditions.

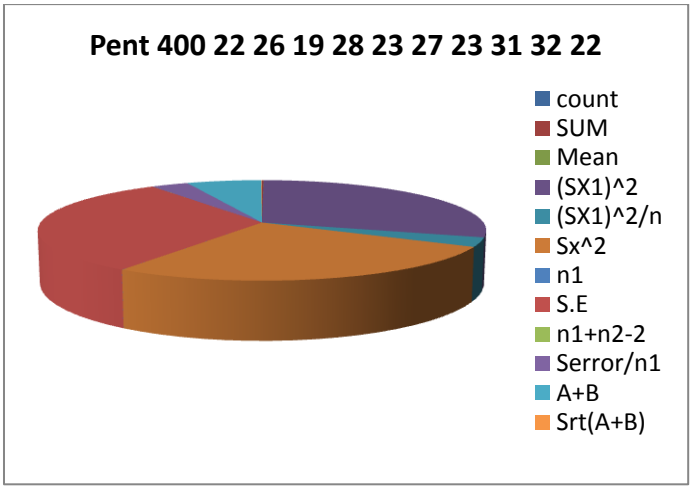
The patients were divided into two groups.

- Group 1 -10 Patients received Pentoxifyl-line (400mg TDS orally for 4 wks)
- Group 2-10 Patients received Placebo for 4 wks

Concurrent use of any other drugs were not allowed. During follow up all the patients were examined clinically and all the investigations were repeated. The study was conducted for 4 wks.

Statistical Analysis

Statistical Analysis was done by student's t-test. The t value is 25.01 with degree of freedom i.e 18. The t value indicates that difference in between two groups of patient is highly significant (P<0.001). Graph 1 shows the statistical representation of Pentoxyfilline therapy.



Graph-1 Statistical representation of Pentoxyfil-line Therapy

RESULT

Higher baseline Maddrey Discriminant Function associated with increased mortality in patients with severe alcoholic hepatitis. Table-1 shows decrease in DF after administration of Pentoxifylline 400mg TDS for 4 wks, which indicates improvement in survival in patients with Maddrey DF ≥ 32. But there no decrease in DF in patients administered Placebo for 4 wks (Table-2). Comparision of DF before and after Pentoxifylline therapy is shown in Graph-2.There is significant decrease in DF in patients with Pentoxifylline (Graph-2).There is no change in DF in patients treated with placebo.(Graph-3)

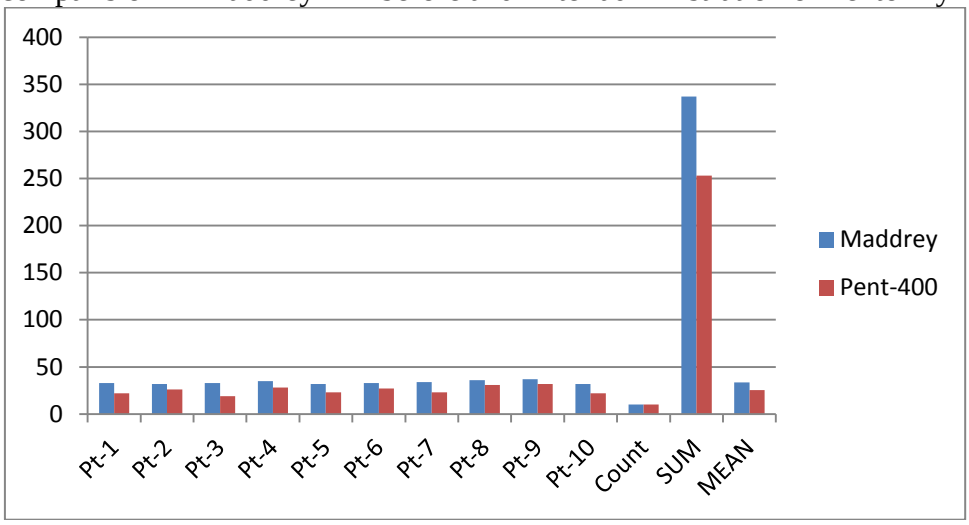
Table-1 shows Maddrey DF before and after Pentoxyfilline 400 therapy

No of Patients	Maddrey DF before start of therapy	Maddrey DF after Pent-400
1	33	22
2	32	26
3	33	19
4	35	28
5	32	23
6	33	27
7	34	23
8	36	31
9	37	32
10	32	22

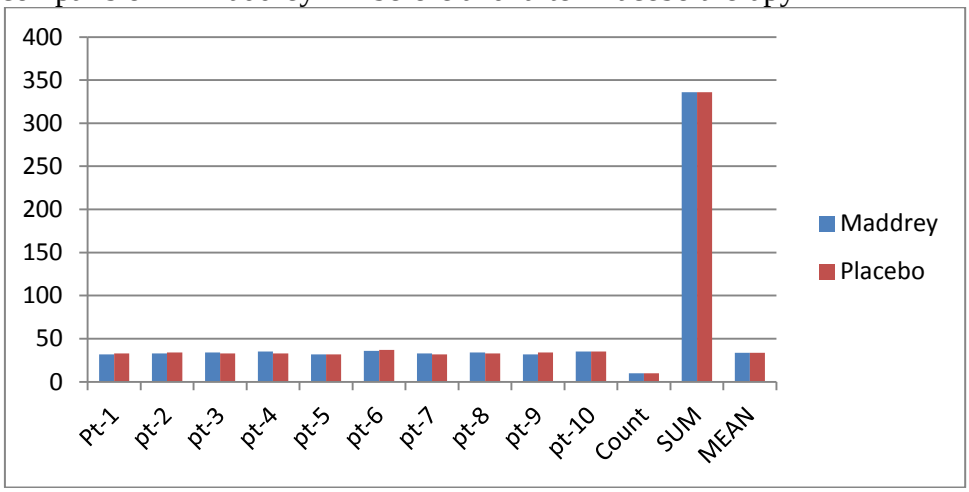
Table-2 shows Maddrey DF before and after Placebo

No Of Patients	Maddrey DF before starting Placebo	Maddrey DF after Placebo
1	32	33
2	33	34
3	34	33
4	35	33
5	32	32
6	36	37
7	33	32
8	34	33
9	32	34
10	35	35

Graph-2 shows comparision in Maddrey DF before and After administration of Pentoxifylline



Graph-3 shows comparision in Maddrey DF before and after Placebo therapy



Discussion

The pathogenesis of alcohol-induced liver disease (ALD) has been unravelled, treatment for patients with this disease will remain an elusive goal. TNF-alfa may play an important role in pathogenesis of ALD.

Pentoxyfilline, non-specific phosphodiesterase inhibitor, with combined anti-inflammatory and antifibrogenic properties, has been shown to block the activation of hepatic stellate cell in culture. [15] It also has inhibitory effect on basic mechanism of fibrogenesis such as cell proliferation and

extracellular matrix synthesis.[16] Pentoxifylline has an added advantage of fewer adverse effects, such as gastrointenstinal bleeding.

Conclusion

As compared to Placebo, Pentoxifylline reduce mortality, improves risk-benefit profile & lowers Maddrey Discriminant Function in patients with severe alcoholic cirrhosis. Hence it is suggested that Pentoxifylline is efficacious in treatment of severe alcoholic hepatitis.

References

1. Hardison WG,Lee FI, Prognosis in the acute liver disease of the alcoholic patients .N Engl J Med 1966;275:61-66.
2. Leevy CM.Cirrhosis in alcoholics. Med Clinics North Am 1966;52:1445-51.
3. Zhang T,Li Y,Lai JP,Douglas SD,Metzger DS,O' Brien CP,Ho WZ.Alcohol potent-iates hepatitis C virus replicon expression. Hepatology.2003;38:57-65.{Pub Med}
4. Spahr L,Giostra E,Frossard JL,Bresson-Hadni S,Rubbia-Brandt L,Hadengue A, Soluble TNF-R1,but not tumor necrosis factor alfa,predicts the 3-month mortality in patients with alcoholic hepatitis.J Hepatol 2004;41:229-234{Pub Med}
5. McCullough AJ,O'Connor JF.Alcoholic liver disease:proposed recommendation for the American College of Gastroenterology. Am J Gastroenterol.1998;93:2022-2036. [PubMed]
6. Maddrey WC,Boitnott JK,Bedine MS,Weber FL Jr,Mezey E,White RI Jr.Corticosteroid therapy of alcoholic hepatitis.Gastroenterology 1978;75:193-6.
7. Sheth M.Riggs M.Patel T (2002)."Utility of the Mayo End-stage Liver Disease (MELD) scores in assessing prognosis of patients with alcoholic hepatitis" BMC gastroenterology2:2.
8. Akriviadis E,Botla R,Briggs W,Han S, Reynolds T,Shakil O (2000), "Pentoxifyl-line improves short term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial" Gastroenterology 119 (6):1637-48.
9. Christensen E.Alcoholic hepatitis-glucocorticoids or not?J Hepatol.2002;36: 547-548.[Pub Med]
10. Agarwal K,Kontorinis N,Dieterich DT. Alcoholic Hepatitis.Current Treat Options Gastroenterol.2004;7:451-458.[PubMed]
11. Haber PS,Warner R,Seth D,Gorwell MD,McCaughan GW.Pathogenesis and management of alcoholic hepatitis.J Gastroenterol Hepatol.2003;18:1332-1344. [PubMed]
12. Strieter R,Remick D,Ward P,Spengler RN,Lynch JP 3rd,Larrick J.Cellular and molecular regulation of tumor necrosis factor alfa production by pentoxifylline. Biochem Biophys Res Commun 1988; 155:1230-6.
13. Bienvenu J,Coulon L,Barbier Y,et al.Study of pentoxifylline induced modulation of TNF alfa and interleukin-6 secretion in healthy and septic patients by the use of an ex-vivo model on whole blood.Nouv Rev Fr Hematol 1992;34 (suppl)S 1-3.
14. Raetsch C,Jia JD,Boigk G,Bauer M,Hahn EG, Riecken EO,Schuppan D. Pentoxifyl-line down regulates profibrogenic cytokinees and procollagen 1 expression in rat secondary billiary fibrosis. Gut. 2002; 50:241-247.
15. Lee KS,Cottam HB,Houglum K, Wasson DB,Carson D,Chojkier M.Pentoxifylline blocks hepatic stellate cell activation independently of phosphodiesterase inhibitory activity. Am J Physiol.1997; 273:G1094-G1100.
16. Windmeier C, Gressner AM. Pharmacolo-gical aspects of pentoxifylline with emphasis on its inhibitory action on hepatic fibrogenesis. Gen Pharmacol. 1997; 29:181-196.