Original Research Paper

Volume - 11 | Issue - 09 | September - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Surgery

EFFICACY OF PROPHYLACTIC *MEROPENEM* IN REDUCING MORTALITY IN "SEVERE" ACUTE PANCREATITIS

Pratik Sharan Junior Resident, Department of Surgery, RIMS Ranchi

Anjay Kumar* Associate Professor, Department of Surgery, RIMS Ranchi *Corresponding Author

ABSTRACT **INTRODUCTION:** One of the major cause of death in cases of severe acute pancreatitis is SIRS and MODS. Prophylactic antibiotics are known to reduce the septic complications in these cases. The aim of this study is to assess the efficacy of prophylactic meropenem in reducing mortality in severe acute pancreatitis. **METHOD:** Patients of severe acute pancreatitis were taken in the study and was randomized into two groups ie, one receiving iv Meropenem 500 mg TDS and other receiving normal saline as placebo; both started at the day of admission, and given for next 14 days. The occurrence of local and septic complications, mortality rate and length of stay were recorded and compared in both groups. **CONCLUSION:** Mortality rate was found significantly less in the group receiving meropenem than placebo. But, no difference were noted in terms of septic and local complications between both groups.

KEYWORDS :

INTRODUCTION:

Sepsis and related complications are the major predictor and cause of mortality in acute pancreatitis, that can be as high as 50%. Therefore, interest has been focused on the prophylactic administration of antibiotic to prevent infections in AP. Several studies conducted in the past 10 years proved that prophylactic antibiotics are helpful in decreasing the incidence of septic pancreatic complications. The carbapenems has a high pancreatic tissue concentration and the highest bactericidal activity against most of the organisms present in pancreatic infections. Meropenem belongs to the same antibiotic family as imipenem but has a number of additional structural features that confer advantages over imipenem in terms of considerable stability to renal dehydropeptidase-I and enhanced activity against gram-negative organisms, including *Pseudomonas aeruginosa.* Meropenem could thus represent a valid alternative to imipenem. Unlike imipenem, it is stable to dehydropeptidase-1, so can be given without cilastin[11]. The aim of this study is to assess the efficacy of prophylactic meropenem in preventing the septic complications in severe acute pancreatitis.

MATERIALS AND METHODS:

Seventy six patients of severe (necrotizing) acute pancreatitis were involved in the study done at RIMS Ranchi in between January 2019 to January 2020.

The criteria for inclusion in the study were age older than 18 years, a diagnosis of severe AP with evidence of pancreatic necrosis in contrast-enhanced CT scan, a normal Serum creatinine, admission within 72 hours of onset of symptoms and no intake of antibiotics in the 3 days before admission.

Informed written consent was obtained by all patients. Simple randomization was used to identify 2 groups of n=38 patients: the first group was treated with 500 mg meropenem intravenously every 8 hours and the second was given placebo with normal saline, both for 14 days after admission. All patients were treated with standard protocol. Extent of necrosis was determined by CECT scan and CTSI. The clinical course of the disease was monitored using routine laboratory tests and sepsis indices like WBC <4000 or >12000 cumm, pyrexia, Respiratory rate <20, heart rate >90 bpm. Also, other systemic parameters were noted in order to exclude SIRS-MODS. Contrast-enhanced CT and ultrasonography were repeated when requested on the grounds of clinical outcome. Severity of the disease was assessed by the Glasgow criteria and the contrast-enhanced CTSI.

Pancreatic infection, extra pancreatic infection, severity of disease, occurance of SIRS, mortality rate and length of hospital stay was recorded and compared in both the groups by using computer aided app Analystat, using Chi- square test. A p-value of <0.05 was taken as statistically significant.

RESULT:

All patients received a standard protocol of treatment and all entities were recorded in both the groups and found that there is no significant difference in the incidence of Septic complications (diagnosed by clinical signs and inflammatory markers) in both the groups ie; 17% in group receiving Meropenem and 16.5% in the group receiving Placebo.

In terms of Local complications, the group receiving Meropenem had an incidence of 24% while that receiving placebo had an incidence of 22%, local complications mostly being Pleural effusion, Acute fluid collection and Pseudocyst; all in descending order. The incidence of SIRS in Meropenem group is found 14% while that in placebo group is 33%, the difference being significant. The incidence of MODS is 11% in meropenem group while 9% in placebo group. Also, the difference in the progressiveness of severity of the disease is almost nil in both the groups. The average length of hospital stay in Meropenem group is 11 days while that in the placebo group is 10 days. Blood culture of both the groups were done and no growth of any organism was observed in both the groups; both at the time of admission (day 0) and at 48 hours, emphasizing no role of antibiotics even in severe acute pancreatitis.

Patient Mortality

The overall mortality rate was 2.6% (2 of 38) in the meropenem group and 10.5% (4 of 38) in the placebo group. The median time from onset of symptoms to death in the meropenem group was 28 days compared with 18 days in the placebo group ($P = 0.972$, by proportional hazards regression). 1st death occurred within 7 days and 2nd between 8 and 14 days. All deaths in both groups were due to disease progression, usually with multi organ failure, either with or without pancreatic infection. There were 13 patients in the meropenem arm and 15 in the placebo arm who had pancreatic infection. Among patients with <30% necrosis 1 of 38 (1.3%) died, also 1 of 38 (1.3%) in patients with >30% necrosis in Meropenem group; whilst in Placebo group, 3 out of 38 (3.9%) died with necrosis >30% and only 1 died out of 38 (1.3%) with necrosis<30%. This proves the judicious use of meropenem in randomised patient groups in decreasing mortality.

Interestingly, there is a significant difference in the mortality rate between both the groups. The group receiving Meropenem had a mortality rate of 2.6% (2 out of 38 died) while that of placebo group is about 10.5% (4 died out of 38), the cause of death mostly being hypovolemic shock with MODS or SIRS. There is no clinical sign of sepsis in patients died in both the groups. Also, there were no growth seen in the blood culture done twice in both the groups, suggesting no role of sepsis in mortality, thus creating a doubt on use of any antibiotic.

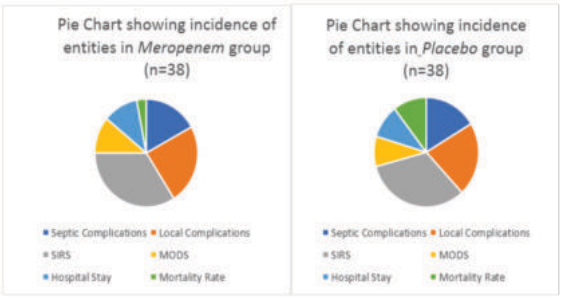
DISCUSSION:

Current understanding supports management of patients affected by severe AP with broad-spectrum antibacterial agents able to treat pancreatic tissue necrosis, such as imipenem or fluoroquinolones. A recent meta-analysis of published randomized, controlled trials concluded that prophylactic antibiotic treatment of patients with severe AP is effective in reducing both the infection rate and the mortality rate. In the this study, we tested antibiotic meropenem, which has, in comparison with placebo in order to compare different entities

like incidence of SIRS, MODS, septic and local complications and mortality rate. Meropenem was generally well tolerated with fewer serious adverse events than the placebo group. In this randomised study, it is seen that Meropenem had proven its efficacy against reducing the mortality rate, in comparison to the placebo group. A previous comparison study of imipenem-cilastatin to nontreatment in patients with necrotizing pancreatitis (n = 74) demonstrated a significant reduction in the incidence of pancreatic infection with treatment but no difference for operations or mortality[2]**.** Another study noted a reduction in both infections and mortality in patients with necrotizing pancreatitis (n = 60) receiving prophylactic cefuroxime compared with the nontreatment group, in a study flawed by apparent problems with intravenous catheter infections and by a unique method for counting infections.[3] A multicenter comparison of pefloxacin and imipenem-cilastatin in patients with necrotizing pancreatitis (n = 60) found a lower incidence of infection with imipenem-cilastatin but no difference between groups in mortality.[4] Two smaller trials (n = 23 and n = 26) also reflect the results of these larger trials[5] Another trial, without a placebo group, showed no additional benefit to continuing imipenem-cilastatin beyond 14 days.[6] More recently, a randomized study conducted in patients with acute necrotizing pancreatitis (n = 58) showed a significant reduction in the *clinical* diagnosis of pancreatic infection without culture or operative confirmation without, however, a reduction in proved infections, actual operations, or mortality rate.[7] Manes et al have reported meropenem to be as effective as imipenem-cilastatin in preventing infectious complications in patients with acute pancreatitis in a randomized, controlled trial (n = 176),[8] but there was no placebo group. The only published double-blind study (n = 114) in acute necrotizing pancreatitis, which had a greatly improved design compared with previous studies, demonstrated no advantage of early antimicrobial (ciprofloxacin and metronidazole) prophylaxis when compared with placebo. In this study, 35 of 76 patients with necrotizing pancreatitis received additional, nonstudy antibiotics (half in the first week) for increasing SIRS or MODS with no significant difference between the antibiotic and the placebo group[9]**.** However, these meta-analyses reached statistical significance only through inclusion of study results, which were biased by a problem with either catheter sepsis or catheter management. These meta-analyses were performed prior to the recent double-blind study by Isenmann et al**,** as was the Cochrane review, which reported that, despite variations in antimicrobial agent used, degrees of necrosis, and duration of treatment, there was strong evidence that antimicrobial prophylaxis decreased the risk of infection and mortality. If the data from Isenmann et al and this report are added to the data in the Cochrane review, then the comparisons between antibiotic and placebo lose statistical significance both for pancreatic infection and mortality. This trial was initiated before the Isenmann et al results were available, but they lend weight to the conclusions of that paper. Unlike the previous studies done which do not concluded about reduction in mortality ; this study clearly shows that the use of meropenem for 14 days shows an effective reduction in the mortality in compared to placebo.

CONCLUSION:

This study showed that judicious use of Prophylactic Meropenem in patients with acute severe pancreatitis can significantly reduce mortality rate in compared to placebo, most likely by reducing sepsis heralded by translocation of gut flora; and also by reducing inflammatory response.



REFERENCES:

1. Keynan S,Hooper NM,Felici A, Amicosante G, Turner AJ (1995). "The renal membrane dipeptidase (dehydropeptidase I) inhibitor, cilastatin, inhibits the bacterial metallo-beta-lactamase enzyme CphA". *Antimicrob. Agents Chemother*. 39(7): 1629–1631.
2. Pederzoli P,Bassi C,Vesentini S, et al. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surg Gynecol Obstet*. 1993;176:480–483
3. Sainio V, Kemppainen E, Puolakkainen P, et al. Early antibiotic treatment in acute necrotising pancreatitis. *Lancet*. 1995;346:663–667.
4. Bassi C, Falconi M, Talamini G, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. *Gastroenterology*. 1998;115:1513–1517.
5. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. *Pancreas*. 1996;13:198–201.
6. Maravi-Poma E, Gener J, Alvarez-Lerma F, et al. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. *Intensive Care Med*. 2003;29:1974–1980.
7. Nordback I, Sand J, Saaristo R, et al. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis: a single-center randomized study. *J Gastrointest Surg*. 2001;5:113–118.
8. Manes G, Rabitti PG, Menchise A, et al. Prophylaxis with meropenem of septic complications in acute pancreatitis: a randomized, controlled trial versus imipenem. *Pancreas*. 2003;27:79–83
9. Isenmann R, Runzi M, Kron M, et al. German Antibiotics in Severe Acute Pancreatitis Study Group. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology*. 2004;126: 997–1008