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Original Research Article

Evaluation of role of granulocyte macrophage colony stimulating factor (GM-CSF) in treatment of patients with perforation peritonitis: a prospective study

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ABSTRACT

Background: GM-CSF has been demonstrated to be effective in reducing the incidence of infection in patients who receive myelosuppressive anticancer chemotherapy or patients who are neutropenic and agranulocytic. We study the role of GM-CSF in non-neutropenic patients with Systemic Inflammatory Response Syndrome (SIRS), infections and sepsis with impaired neutrophil function to access the current rationale for administering GM-CSF in addition to standard antibiotic therapy to critically ill patients

Methods: All patients undergoing surgery for peritonitis due to gastrointestinal perforations were included in this study and were divided into two groups alternatively to avoid any bias i.e. Group A 1, 3, 5 etc. and Group B 2, 4, 6 etc. Group A - all patients received GM-CSF along with standard antibiotics. Group B patients received antibiotics only. Course of patient in immediate postoperative period, time to improvement, duration of hospital stay, antibiotic therapy, rate of complications were compared.

Results: Patients in group A had a lower duration of antibiotic therapy and hospital stay. Patients in group A took less time to show clinical improvement compared to patients in Group B. Group A also had a much lower rate of infectious and systemic complications compared to group B.

Conclusions: Results of the present study show that GM-CSF is an important molecule when used as adjunct to antibiotics in cases of abdominal sepsis. Use of this growth factor is associated with less incidence of septic complications and morbidity, a shorter duration of antibiotic therapy and hospital stay without significantly compromising the cost. The results of present study help in identifying its role in non-neutropenic patient groups who are most likely to benefit from its administration.

Keywords: Colony stimulating factors, GM-CSF, Perforation peritonitis, SIRS

INTRODUCTION

Intra-abdominal infections are commonly encountered in surgical practice where prompt and effective decision-making is critical. Delay in treatment risks physiological deterioration because of activation of local and systemic inflammatory responses. The severity of intra-abdominal infections and the poor prognosis of patients with such inflammation have led to the development of several therapies such as radical debridement, lavage systems, open management, planned re-operation etc. Despite major advances in antimicrobial therapy and supportive

care, the morbidity and mortality of generalized peritonitis still remain high and there has always been a search for some alternative or supportive treatment.[1] Granulocyte macrophage colony-stimulating factor (GM-CSF) is a specific hematopoietic growth factor extensively used for the treatment of neutropenia after chemotherapy.[2] In vitro, GM-CSF stimulates the proliferation and differentiation of hematopoietic precursor cells as well as several functional activities of mature granulocytes. In vivo, it increases circulating white blood cells. In recent years, GM-CSF has been demonstrated to be effective and safe in reducing the incidence of infection in high-risk patients like those who receive myelosuppressive anticancer chemotherapy or patients who are neutropenic and agranulocytic.[3] However, the role of GM-CSF in non-neutropenic patients with Systemic Inflammatory Response Syndrome (SIRS), infections and sepsis with impaired neutrophil function has not been well studied.

Aim of this study was to access the current rationale for administering GM-CSF in addition to standard antibiotic therapy to critically ill patients, at risk of or with sepsis/SIRS, to improve neutrophil function and to modulate the otherwise predestined release of inflammatory mediators. Thus, by direct and indirect effects, GM-CSF may prevent the fatal course of sepsis in these critically ill patients and promote recovery. This prospective study was conducted to assess the exact role of GM-CSF in patients of perforation peritonitis in a tertiary care institute.

METHODS

This prospective study was conducted on 50 patients of perforation peritonitis, admitted in surgical wards of Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. All patients undergoing surgery for peritonitis due to gastrointestinal perforations were included in this study after taking written informed consent and were divided into two groups alternatively to avoid any bias i.e. Group A - 1, 3 ,5 etc. and Group B - 2, 4, 6 etc. In Group A all patients received GM-CSF along with standard antibiotics. Group B patients received antibiotics only.

Intervention

The standard antibiotic therapy consisting of Ceftriaxone sodium (1 gm twice daily), Amikacin (15 mg/kg/day) and Metronidazole (500 mg thrice daily) was started before surgery in all patients and continued for five to seven days depending upon clinical status (normalization of temperature and white blood cell count) of the patient. Antibiotic treatment was modified according to antimicrobial susceptibility of the organism isolated, if required. According to random allocation schedule, GM-CSF was administered, in Group - A patients, 5µg/day subcutaneously for three days along with the above said antibiotics beginning from the day of operation.

Inclusion criteria

All patients, aging 15-75 years of either sex with generalized peritonitis at the time surgical intervention were included in the study.

Exclusion criteria

Patients of peritonitis with terminal renal, hepatic or lung failure or patients receiving treatment with immunosuppressive drugs etc. were excluded from the study.

Measurements and data analysis

Clinical data regarding age, sex, duration of illness, time of presentation and presenting symptoms were noted along with findings of general physical and abdominal examinations and were recorded in the patient's proforma. Detailed operative findings of all the patients were also recorded at the time of exploratory laparotomy in both groups. Specific investigations required were culture sensitivity of peritoneal fluid at the time of exploration and TLC/DLC counts in postoperative period. Clinical evaluation and specific investigations such as TLC/DLC counts were performed on a daily basis during hospital stay and every 2 weeks after discharging up to 2 months.

Following clinical outcomes were recorded:

- Course of patient in immediate postoperative period
    1. Stable/unstable
    2. Inotrope support needed/not needed
    3. Respiratory support needed/not needed
- Time to improvement i.e. improvement in abdominal signs and appearance of bowel sounds
- Duration of antibiotic treatment for abdominal sepsis and/or infectious complications
- Duration of hospital stay
- Emergence of complications, mortality, adverse reaction to drugs.

All these factors in both the groups were recorded and compared with standard statistical methods. A commercial software package was used to analyse the data. Continuous variables were summarized in terms of mean±SD or median. The nominal data were compared by Chi-square test. The 2-tailed t-test for independent samples was used to compare means, and the Mann-Whitney test was used to compare medians. P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 patients with generalized peritonitis were studied and divided into two group by randomizing alternatively. Group A patients received GM-CSF along with the standard antibiotics while Group B patients received antibiotics only. Baseline demographic

characteristics, laboratory tests and intraoperative diagnosis were statistically comparable in both the groups (Table 1). Mean age of the patients was 39 years in group A and 42.96 years in group B, with majority of the patients being male in both the groups. 20% of the patients in group A and 32% in group B were in the age group of more than 50 years.

Table 1: Baseline characteristics.

Parameter	Group A (n = 25)	Group B (n = 25)
Sex, M/F	23/2	21/4
Age, Mean±SD	39±14	42.96±11.07
Signs and symptoms		
Pain	25	25
Vomiting	25	25
Fever	11	10
Abdominal distention	18	14
Constipation	25	25
Shock	3	5
Investigations		
WBC count/µl, mean±SD	11.22±6.65	9.98±3.45
Neutrophil count/µl, Mean±SD	72.84±11.16	77.96±9.61
Pneumoperitoneum on chest X-ray	23	21

The clinical presentation of the patients varied according to the site of perforation. The patients of duodenal perforation usually had a short history of pain starting in upper abdomen along with generalized tenderness and guarding while the patients with small bowel perforation presented with prolonged history of fever followed by pain in lower abdomen.

Table 2: Operative data.

Parameter	Group A (n=25)	Group B (n=25)
Site of perforation		
Gastric	2	1
Duodenum	13	12
Ileum	9	12
Colon	1	0
Nature of exudates -		
Clear	13	13
Purulent	7	4
Fecal	5	8
Surgical procedure -		
Simple closure	15	12
Enteroplasty	5	1
Resection and anastomosis	1	4
Ileostomy	4	8

Pain abdomen and vomiting were constant symptoms present in all patients of both groups. Fever was present in 44% cases in group A and 40% cases in group B, while abdominal distention was seen in 72% patients in group A and 56% in group B (Table 1). Out of the 50 patients, eight patients presented with features of shock at the time of admission (three in group A, 5 in group B). On chest X ray, 92% cases in group A and 84% cases in group B had evidence of pneumoperitoneum.

In the present study, duodenum was the commonest site of perforation (52%) followed by ileum (36%) in group A patients, while duodenum and ileum had equal incidence (48% each) in group B. In majority of patients, the peritonitis was generalized, and contamination was wither purulent or fecal. The other operative findings and surgical procedures performed are as illustrated in Table 2.

Table 3: Clinical outcomes.

Outcome	Group A (n=25)	Group B (n=25)	p value
Time taken to improve (median, days)	2	3	0.02
Time with antibiotics (median, days)	5	7	<0.001
Hospital stay (median, days)	7	9	0.02
Infectious complications (no.)	5	15	0.002
Surgical wound infection	3	8	
Wound dehiscence	1	4	
Intra-abdominal abscess	1	3	
Systemic complications (no.)	7	16	0.011
Pleural effusion	3	6	
Pneumonia	2	5	
Respiratory failure	0	2	
Pulmonary embolism	1	0	
Superficial phlebitis	1	0	
DVT	0	1	
Sepsis and multiorgan failure	0	2	
Re-operations (no.)	0	1	
Deaths (no.)	1	4	0.157

After 48 hours of treatment, WBC count showed a gradual increase in group A patients. On day three, mean WBC count was 14.91 x 10^3/µl in group A and 9.64 × 10^3/µl in group B (p <0.001) patients. On day five, mean WBC count was 13.42 × 103/µl in group A and 8.52 × 10^3/µl in group B (p<0.001) patients respectively. WBC values returned to normal in both groups in the second

week and remained so in follow up. Median time for clinical improvement was two days in group A and three days in group B ($p<0.05$). Median hospital stay was seven and nine days ($p<0.05$) and median time with antibiotic therapy was five and seven days ($p<0.05$) respectively (Table 3).

Five episodes of infectious complications developed in group A and 15 in group B ($p = 0.002$). Wound infection was the commonest complication seen (three and eight respectively). Wound dehiscence was observed in one patient in group A and three patients in group B. Wound infection and wound dehiscence were managed by daily antiseptic dressings in most of the patients. One patient in group B needed secondary suturing for closure of the laparotomy wound. One patient in group A has residual intra-abdominal abscess (presence of fluid collection detected by ultrasound or CT scan with a positive blood culture) which was managed by intravenous antibiotics only. Three patients in group B has residual abscess, two of them required ultrasound guided aspiration of the abscess.

Seven patients developed systemic complications in group A and 16 in group B. Pleural effusion was the commonest complication seen (three vs six). In group A, two cases of pneumonia, one case of pulmonary embolism and superficial phlebitis were observed. In group B, five cases of pneumonia, two cases each of respiratory failure and sepsis related multiorgan failure and one case of deep vein thrombosis were seen. Few side effects of molgramostim administration like nausea and skin rashes were observed in three patients in group A. One patient in group A had anastomotic leak was re-explored subsequently.

There was one death in group A and the cause of death was pulmonary embolism while four patients died in group B, the causes being refractory shock, respiratory failure in two and sepsis leading to multiorgan failure in the other two.

DISCUSSION

During the past 3 decades, the incidence of colorectal Peritonitis due to perforation of gastrointestinal tract is one of the most common surgical emergencies all over the world and continues to be a major problem confronting surgeons with a mortality rate of upto 60% in some studies.[4] Outcome has been found to be related mainly to host factors (e.g. preoperative nutritional status, organ impairment, the severity of the patient's systemic response, and the premorbid physiological reserves predicted by APACHE II scoring system) rather than to type and source of the infection.[5,6] Despite advances in surgical techniques, antimicrobial therapy and intensive care support, management of peritonitis continues to be highly demanding, difficult and complex. In countries like India, it more commonly affects young men in their prime of life as compared to the studies in the west where the mean age is 45-60 years.[7] In majority of the cases, presentation to the hospital is late with well-established generalized peritonitis, purulent/faecal contamination and varying degrees of septicemia.[8] It is necessary to recognize patients at risk preoperatively and prepare for an intensive postoperative management strategy.

Most of the patients in our study had perforation of upper gastrointestinal tract most commonly of duodenum (52% vs 48%) followed by distal ileum as has been noted in earlier studies from India, which is in sharp contrast to studies from developed countries where distal gastrointestinal tract perforations are more common.[9,10] Not only the site but the etiological factors also show a wide geographical variation. Peptic ulcer, typhoid and tuberculosis are common causes of perforation peritonitis in our set up while diseases like appendicitis, diverticulosis are the common causes of perforation in western world.[11,12]

Present results show that addition of GM-CSF to the standard antibiotic treatment of patients with perforation peritonitis is safe and effective, reducing the rate of infectious and systemic complications, duration of antibiotic therapy and length of hospital stay. This is only the second trial, after the study of Orozco et al, to evaluate the clinical efficacy of GM-CSF in abdominal sepsis in humans and a first in our country.[13] It has been observed experimentally that GM-CSF has several effects in peritonitis, such as enhancement of haematopoiesis and immune reaction and it may also play a role in the down-regulation of inflammatory mediators that are produced by bone marrow cells during abdominal sepsis.[14] It is well know that GM-CSF enhances many of the granulocyte and monocyte-macrophage functions, such as the generation of superoxide anion in response to bacterial peptides, among many others.[15] GM-CSF has been shown to enhance the migration and proliferation of endothelial cells and to promote keratinocyte growth contributing to the healing process.[16] Arnold et al conducted a trial in which 10 patients were treated with four intradermal injections of molgramostim at 50 µg around the perimeter of their ulcers every two weeks for a total of 12 weeks. No haematological abnormalities were observed, and the injections were relatively painless. Although this study was not designed to determine efficacy, some patients demonstrated complete or partial healing of their ulcers.[17]

In a randomised, placebo-controlled trial involving 40 patients with diabetic foot infections, Gough et al evaluated the effect of granulocyte colony-stimulating factor, as adjuvant therapy. They found that this treatment induced statistically significant differences in terms of earlier eradication of pathogens from infected ulcers ($p = 0.02$), quicker resolution of soft tissue infections, shorter hospital stay, shorter duration of intravenous antibiotic treatment, and increased neutrophil production.[18] In another study, in neutropenic patients with bacterial and fungal infections, treatment with antibiotics plus GM-

CSF resulted in a significantly better response rate than antibiotics plus placebo.[19]

Presnell et al, conducted a randomized, double-blinded, placebo-controlled study where they added low-dose (3 mcg/kg) intravenous recombinant human GM-CSF daily for five days to conventional therapy in 10 patients, with a further eight patients receiving placebo. GM-CSF treated patients showed improvement in $Pa(O_2)/Fi(O_2)$ over five days ($p = 0.02$) and increased peripheral blood neutrophils ($p = 0.08$), whereas alveolar neutrophils decreased ($p = 0.02$). They concluded that low-dose GM-CSF was associated with improved gas exchange without pulmonary neutrophil infiltration, despite functional activation of both circulating neutrophils and pulmonary phagocytes. In addition, GM-CSF therapy was not associated with worsened acute respiratory distress syndrome or multiple organ dysfunction syndrome, suggesting a homeostatic role for GM-CSF in sepsis related pulmonary dysfunction.[20]

Results of the present study were consistent with those reported by Orozco et al and others.[13,21,22] Administration of GM-CSF together with antibiotics induces a progressive and significant rise in white blood cell count and neutrophils. The observed improvement in clinical outcomes in term of lower number of infectious and systemic complications, shorter hospital stay, faster clinical improvement, and shorter duration of antibiotic therapy is also consistent with published evidence that colony stimulating factors may be of great help in patients with infectious diseases associated with neutropenic and nonneutropenic conditions.[23] Few side effects during GM-CSF administration like nausea and skin rashes were observed in the study group that disappeared once treatment was suspended. This low incidence of side effects was also observed in the study by Dierdof et al.[22]

In conclusion, the results of the present study shows that GM-CSF is an important molecule when used as adjunct to antibiotics in cases of abdominal sepsis. Use of this growth factor is associated with less incidence of septic complications and morbidity associated with them. In our study it was found to be useful in terms of less number of septic and systemic complications, lesser duration of antibiotic therapy and shorter duration of hospital stay. But since this factor is expensive, the cost-benefit analysis is also required. The use of this factor saves the cost of patient in terms of shorter requirement of costly intensive care settings, decreased use of costly antibiotics etc. So, it ultimately proves worth by reducing overall morbidity and mortality of the patient without significantly compromising the cost. Thus GM-CSF is an important molecule, the role of which has been established in enhancing hematopoietic recovery after cancer chemotherapy and bone marrow transplantation. The results of present study further help in identifying its role in non-neutropenic patient groups who are most likely to benefit from its administration with respect to infection resolution as well as reduction of septic complications. Further studies to confirm these results would be desirable in future.

CONCLUSION

Results of the present study show that GM-CSF is an important molecule when used as adjunct to antibiotics in cases of abdominal sepsis. Use of this growth factor is associated with less incidence of septic complications and morbidity, a shorter duration of antibiotic therapy and hospital stay without significantly compromising the cost. The results of present study help in identifying its role in non-neutropenic patient groups who are most likely to benefit from its administration.

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