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Original article

Comparative study of three antimicrobial drugs protocol (Ceftriaxone, Gentamicin/Amikacin and Metronidazole) *versus* two antimicrobial drugs protocol (Ceftriaxone and Metronidazole) in cases of intra-abdominal sepsis

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Abstract

Background: Treatment of intra-abdominal sepsis with antibacterial drugs should be initiated as soon as possible diagnosis is made before surgery and continued in the post operative period, unless required to be changed (when there is no satisfactory clinical response). The ideal agent (s) and duration of therapy remains somewhat controversial. However, early experimental and subsequent clinical studies have indicated that the spectrum of chosen antibacterial activity must encompass both colonic aerobes and anaerobes including *B. fragilis.* There are a number of multi drug protocols that are used to treat intra-abdominal septic conditions. Empiric use of these protocols not only adds toxicity to already ill patient but therapy becomes costly and utilizes human resource, unnecessarily. **Aim of study:** To study the clinical efficacy of the treatment of intra-abdominal sepsis with protocol –A (Ceftriaxone, Metronidazole and aminoglycoside) versus protocol –B. (Ceftriaxone and Metronidazole). **Material and methods:** This is a prospective randomized study conducted at NGMC, Nepalgunj, Nepal (2003-2004) on the patient attending for the treatment of intra -abdominal sepsis. Patients included in this study were of inflammation, obstruction with or without gangrene and perforation of appendix, small bowel and large bowel with localized or generalized peritonitis. These patients were managed surgically by- appendicectomy, closure of perforation, resection and anastomosis (R&A) and resection and proximal colostomy. Patients of large bowel obstruction without gangrene and small bowel gangrene were managed by R&A. These patients had significant faecal spillage at the surgical site as well as in the peritoneum. At the end of operation peritoneum and surgical site of all cases were washed with saline and povidone-iodine solution. They were put on one of the two protocols for post-operative treatment. A total 59 patients were included in this study. 32 cases were treated with protocol- A and rest 27 cases were treated with protocol- B. These cases were selected randomly for this study. Their outcome was compiled and compared under following headings: postoperative recovery, postoperative pyrexia, wound infection and dehiscence, anastomotic leak, residual abscess and cost of therapy. **Statistical analysis:** Statistical analysis was done with the help of Chi square test. **Result:** Of the 59 patients, 32 were randomized to group I, 27 to group II. These groups were comparable in age, weight, sex and duration of therapy. Uneventful recovery was noted in 87.5 % (28/32) in -group I where as in 70.37% (19 /27) in-group II. Complications were observed in 12.5% in-group I where as 29.63 % in-group II. 10 patients in-group I where as 7 patients in -group II had surgical site infections (SSIs). All of these had superficial wound infection with/or without dehiscence of small portion of wound. A single case of residual abscess and anastomotic leak was observed. Postoperative pyrexia was noted in 8 patients in-group I where as in 6 patients in-group II. In pyrexia, temperature ranged from 99-104 ^{0}F. Finally except one case, rest of the cases recovered. On follow up after 3weeks, the cases recovered were doing well. **Conclusion:** At least three conclusions can be drawn from this study. Firstly protocol A is equally effective as protocol B. Secondly; it appears that combining aminoglycoside with Ceftriaxone therapeutically has no significant (P=0.09) benefit over Ceftriaxone alone. Finally protocol A is less expensive in terms of total therapy than protocol B and can be used without fear even in subnormal functioning kidney.

Key Words: Comparative Study, Antimicrobial Drugs, Protocol, Intra-abdominal Sepsis

Intra abdominal infections are among the most difficult infections to diagnose early and treat effectively. These deep-seated infections generally occur after the continuity of the gastro- intestinal tract is interrupted by trauma, intrinsic disease or surgery. The leakage of endogenous micro flora into

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adjacent tissue appears to overwhelm the host defense mechanism, resulting in infection. The degree of peritoneal infection dissemination depends upon five factors namely location and size of primary leak, nature of underlying injury or disease, presence of peritoneal adhesions from previous disease or surgeries, the duration of present illness, the efficacy of the local and systemic host defense mechanism [1].

Peritonitis resulting from visceral inflammation or perforation is polymicrobial, which contains anaerobic and aerobic nature of bacterial flora [2,3]. The number of bacterial flora isolated depends on the nature of the micro flora of the diseased or traumatized organ. The common aerobes isolated includes, Klebsiella, E. Coli, Proteus, Streptococcus and enterobacter species, where as common anaerobes most frequently isolated are bacteroides, peptostreptococcus and clostridium species. Although, many bacteria are involved in peritonitis, the most important are E. Coli and *B. fragilis.* They act synergistically with E. coli, responsible primarily for peritonitis, septic shock and early lethality where as *B. fragilis*, for intra-abdominal abscess formation [4,5]. Peritonitis requires draining the abscess, cleaning the peritoneal cavity and eliminating contamination. Antibiotics play a secondary but important role.

Ceftriaxone is a cephalosporin belonging to the third generation; it has a broad spectrum of action, good stability against beta lactamase, long half-life and a good capacity of diffusion into the tissues. It is now considered a reference drug to prevent post surgical nosocomial infections. Present data available on Ceftriaxone dealing with microbiology, pharmacokinetics, (long half- life, tissue penetration ability, tissue concentration present during vulnerable period even after stopping the treatment etc.), result of clinical trials and World Wide experience seem to be in favour of Ceftriaxone as antimicrobial of choice for treatment of severe infection as well as in prophylaxis. [6,7]

Combination antibiotic therapy has been used to provide the patient with broad-spectrum coverage against the many potential pathogens encountered in abdominal trauma. Several potential benefits of the clinical use of antibiotic combinations have been advanced. These include expansion of spectrum of either agent alone allowing treatment of polymicrobial infections and prevention of emergence of antibiotic resistant organism, reducing the potential for toxicity with aminoglycosides and other agents with demonstrated in vitro synergistic activity or additive affect; more effective treatment of bacteraemia in neutropenic patient [8].

In vitro, the synergistic activity of third generation cephalosporins (Cefotaxime, CTX) and aminoglycoside was particularly evident with members of enterobacteriacae. Similarly CTX and dCTX alone and in combination demonstrate synergistic in vitro activity with aminoglycoside against many gram-negative bacteria particularly members of the entero-bacteriace. [9,10] The clinical significance of such interactive synergy is yet to be determined, warrants further investigation [9]. But in clinical study, combination of antimicrobials has not shown to be better than single agent therapy with Cephalosporins [11]. Despite consensus popularity, the "shot gun "approach has not been shown to be better than broad spectrum single agent antimicrobial coverage [12-18]. This study is conducted to evaluate the clinical efficacy of three antibacterial drug protocol, protocol –A versus two antimicrobial drug protocol, protocol –B in the treatment of intra abdominal sepsis.

Material and methods

This is a prospective randomized study conducted at NGMC, Nepalgunj, Nepal (2003-2004) on the patient attending for the treatment of intra abdominal sepsis. Patients included in this study were of inflammation, obstruction with or without gangrene and perforation of appendix, small bowel and large bowel with localized or generalized peritonitis. These patients were managed surgically by- appendectomy, closure of perforation, resection and anastomosis (R&A) and resection and proximal colostomy. Patients of large bowel obstruction without gangrene and small bowel gangrene, who were managed by R&A, had significant faecal spillage at the surgical site as well as in peritoneum. At the end of operation peritoneum and surgical site of all cases were washed with saline and povidone –iodine solution. These patients were resuscitated initially and subjected to appropriate surgical treatment after proper investigation. They were put on one of the two (A or B) protocols for post-operative treatment. 32 cases treated with protocol A and another 27 cases treated with protocol B were selected randomly for this study. Their age, sex, weight, duration of symptoms and daily postoperative progress, complications and final results of the treatment were compiled. Protocol A consists of Ceftriaxone, amino glycoside (Gentamicin/Amikacin) and Metronidazole while protocol B consists of Ceftriaxone and Metronidazole. Their outcome was compiled and compared under following headings: postoperative recovery, postoperative pyrexia, wound infection and dehiscence, anastomotic leak, residual abscess and cost of therapy.

Aim of study

To study the clinical outcome of the treatment of intra abdominal sepsis with protocol – A and protocol –B. (Protocol –A consist of three antimicrobial drugs viz. Ceftriaxone, amino glycoside and Metronidazole. Protocol-B consist of Ceftriaxone and Metronidazole.)

Results

Table 1. Distribution of cases in different age group

Age / Years	Group I*	Group II**
10-19	6	6
20-29	13	4
30-39	7	7
40-49	2	4
>50	4	6
Total	**32**	**27**

Table 2. Sex wise distribution of the patients

Sex	No of patients in Group-A	No of patients in Group- B
Male	21	21
Female	11	6
Total	**32**	**27**

Table 3. Duration of symptoms

Duration of symptoms	Group I	Group II
0-12 hr	Nil	Nil
13-24 hr	5	6
25-48 hr	4	7
49-72 hr	4	5
> 72 hr	19	9
Total	**32**	**27**

Table 4. Distribution of weight in different group

Weight (Kg.)	Group I	Group II
<20	Nil	Nil
20-29	2	1
30-39	2	3
40-49	11	10
>50	17	13
Total	**32**	**27**

Table 5. Causes of intra abdominal sepsis

Appendix		
Acute appendicitis	11	07
Appendicular gangrene	02	02
Appendicular perforation	09	08
Small bowel		
Obstruction with gangrene Perforation	06	02
Colon		
Perforation (traumatic)	01	03
Intussusceptions	01	01
Malignancy colon with perforation	01	01
Pyoperitoneum (Gynaecological causes)	01	03
Total	**32**	**27**

Table 6. Drugs used in two groups

Group	Protocol	Drugs and dosage*
I	A	Ceftriaxone 1gm x iv x bid, Metronidazole 500mg x iv x t id, aminoglycoside (Gentamicin/ Amikacin) 80mg/500mg x iv x bid,
II	B	Ceftriaxone 1 gm x iv x bid, Metronidazole 500mg x iv x t id,

Table 7. Result of therapy

Recovery	Group I no. of cases (%)	Group II no. of cases (%)
Uneventful	18(87.5%)	19(70.37%)
Complications	14(12.5%)	08 (29.63%)
Wound infection	10	07
Post operative pyrexia	07	6
Special problem (prolonged hypo tension)	Nil	1
Total	**32**	**27**

Statistical analysis was done with the help of chi square test (P=0.09)

Table 8 . Distribution of pyrexia

No.	Wound Infection	Post Operative Days →													
Group I		**Temperature (axillary) ↓**													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	SSI	100	98-99 ^{0}F (Normal body temperature)								D				
2	SSI	100	100	100	100	98-99 ^{0}F (Normal body temperature)					D				
3	—	100	100	98-99 ^{0}F (Normal body temperature)						D					
4	—	98-99 ^{0}F (Normal body temperature)			101	98-99 0F (Normal body temperature)									
5	—	100.5	98-99 ^{0}F (Normal body temperature)							D					
6	—	100	100	98-99 ^{0}F (Normal body temperature)								D			
7	SSI	102	98-99 ^{0}F (Normal body temperature)						D						
8	SSI	100	98-99 ^{0}F (Normal body temperature)						D						
Group II															
1		101	100.5	100	100	99	99	100	98-99 ^{0}F (Normal body temperature)		D				
2		100	99	100	99	98-99 ^{0}F (Normal body temperature)					D				
3		101	98-99 ^{0}F (Normal body temperature)								D				
4	SSIs with anastomotic leak	101	98	98	98	104	103	103	101	98	98	101	98	104	L*AMA
5	Drain site infection	101	101	101	98-99 ^{0}F (Normal body temperature)						D				
6	SSI(on 15th day)	101	101	101	98-99 ^{0}F (Normal body temperature)		101	101	98-99 ^{0}F (Normal body temperature)			D			

*LAMA= left against medical advise D= discharged

Table 9. Summary of Demographics Characteristic of 59 patients treated With Two antibiotic Regimen

Antibiotic treatment group		
	Protocol A/Group I	**Protocol B/Group II**
Number of patients	**32**	**27**
Age (yrs)		
Mean	**30.18**	**34**
Range	**13-55**	**14-68**
Standard deviation	**12.24**	**15.71**
Sex		
Male	**21**	**21**
Female	**11**	**6**
Weight (kg)		
Mean	**50**	**50.92**
Range	**25-81**	**29-75**
Standard deviation	**12.9**	**12.8**
Causes of intra abdominal sepsis		
Appendix Acute appendicitis Appendicular gangrene Appendicular perforation	 11 02 09	 07 02 08
Small bowel Obstruction with gangrene Perforation	 06	 02
Colon Perforation (traumatic) Intussusceptions Malignancy with perforation	 01 01 01	 03 01 01
Pyoperitoneum (Gynaecological causes)	01	03
Total	**32**	**27**

Table 10. Severe Intra Abdominal Infection: Summary of the antibacterial Therapy and monitoring of 59 patients treated with two Antibacterial Regimen

	Protocol-A	**Protocol- B**
Number of patients	**32**	**27**
Antibiotic therapy		
Duration of therapy		
Total	**343**	**260**
Mean	**10.7**	**9.6**
Dosing		
Total Number of doses	**23968**	**1296**
Mean daily doses		
Ceftriaxone (gm)	**2**	**2**
Metronidazole (500mg)	**1500**	**1500**
Gentamicin/ Amikacin(mg)	**160/1000**	**--**

Table 11. Comparative cost analysis between two regimens

	Protocol-A Ceftriaxone + aminoglycoside* + Metronidazole	**Protocol-B** Ceftriaxone + Metronidazole
No of patients	32	27
Antibacterial Doses	490	378
Antibacterial Cost (NRS) Ceftriaxone Metronidazole Gentamicin (19 Pt) Amikacin (1 3 Pt) Average Cost of Aminoglycosides	 130.0 / dose 17.0/dose (13.80/dose) 524.4 (53.0/dose) 1378.0 30.68/dose	 130/dose 17.0/dose
Total Antibacterial Cost	83390.72	58779.00
Total Therapy Cost of Syringe & Needle	4480.00	1890.00
Total Cost of Therapy including syringes and needles	87870.72	60669.00
Mean Cost/Patient	2745.96	2247.00
Mean Therapy Cost/Day	**392.28**	**321.00**

* aminoglycoside = Gentamicin/ Amikacin

Of the 59 patients, 32 were randomized to group I rest 27 to group II. These groups were comparable in age, weight and sex (Table VIII) Patients clinical demographics are outlined in table I-VIII. Both the groups were not different in term of followings; age, sex, no of organ involved. But they were different in their severity and duration of the symptoms (Table III). Both the groups were almost similar in the duration of therapy (Table IX). The number of antibacterial drugs were administered corresponds to dose frequency and number of antibacterial utilized (Table IX). 28 patients recovered uneventfully in-group –I whereas 19 patients in-group II. Complication was observed in 14 patients (12.5%) in-group I while in 7 patients (29.63 %) in-group II. All of these patients had superficial wound infection with/ without dehiscence of small portion of wound. A single case of residual abscess and anastomotic leak was observed. Postoperative pyrexia was noted in 8 patients in-group I and in 6 patients in-group II. In pyrexia, temperature ranged from 99-104 F^0. Finally except one case rest of the cases recovered. On follow up after 3weeks recovered patients are doing well. All of the patients required multiple fluid transfusions as well as some of them required blood transfusion

Cost analysis:

Total cost of therapy receiving Ceftriaxone, Metronidazole and aminoglycoside (protocol-A) and Ceftriaxone and Metronidazole (protocol-B) are presented in table-X. The two regimen ranked in term of cost of therapy per patients. : Ceftriaxone, Metronidazole and aminoglycoside > Ceftriaxone and Metronidazole. Over all three-drug combination was 18% more expensive in term of cost of therapy per patients than two drug regimen. Administration costs have not been included in these calculations.

Discussion

Antibiotics should be used prophylactically before contamination has occurred. This is not possible in patients where the infection is already established. In these situations the use of antimicrobial drugs to prevent the growth of bacteria which occurs due to disease / trauma is therapeutic rather than prophylactic.

The effectiveness of antimicrobial therapy in reduction in the incidence of infection in trauma patient has been established in a number of clinical studies [12-18]. Inflammation of gut perforation peritonitis due to small bowel, appendix, large bowel, imposes high risk of septic complication [19-22]. Antimicrobial therapy for patients with inflammation or peritonitis is therapeutic rather than prophylactic because antibiotic is administered after contamination has occurred. In the 1940s the use of penicillin was associated with a 30–40% decrease in mortality rates in penetrating abdominal trauma with peritonitis[17]. Subsequent use of broad-spectrum antimicrobial regimen has been associated with

reduced morbidity rates for abdominal trauma and peritonitis in the range of 4–15%[12-19]. This reduction was due to one of the most exciting & rewarding microbiological observation in 1970 of the role of human anaerobic endogenous micro flora in abdominal infection. Due to polymicrobial nature of the bacterial flora, broad-spectrum antimicrobial coverage has been considered a necessity[17-22, 23]. Agents that are directed against aerobic gram negative bacilli includes- aminoglycosides, II[nd] and III[rd] generation Cephalosporins, monobactams, carbapense, carboxy penicillin, acylapenicillin and either ampicillin or ticarcillin combined with β - lactamase inhibitor (i.e. sulbactam & culvulanic acid) [4]. In vitro studies of anaerobic susceptibility demonstrates no resistance to metronidazole & chloromphenicol, <1% resistance to imipenem – cilastin, ticarcillin, clavulanate, ampicillin – sulbactum and cafaperazone – sulbactam. In vitro resistance rate to cefoxitin and clindamycin were 8% - 3% respectively [8].

Empiric use of Combinations of many antibacterial, were also associated with the emergence of resistant organism as well as serious toxicity and spiraling therapy costs. Despite consensus popularity the "shot gun" approach has not been shown to be consistently better than broad-spectrum single agent antimicrobial coverage[12-19]. Later on a number of prospective studies comparing Gentamicin & Clindamycin *Vs* single agent therapy with III[rd] generation Cephalosporin with poor coverage in patients with complicated appendicitis have noted treatment failure associated with *β. fragilis*.[25-27]

In the present study our results indicates that the clinical efficacy of Ceftriaxone, Gentamicin/Amikacin and Metronidazole (three drug protocol) is not (p=0.09) significantly better than Ceftriaxone and Metronidazole (two drug protocol). Previous workers in their study also reported similar results.[19]

Apart from addition of cost of therapy and nephrotoxicity of Gentamicin/ Amikacin, it takes 3-4 days of administration to attain the effective serum concentration. Probably this may be the reason that GM is not very much effective in vivo as it is shown in vitro studies. [8]

Conclusion

At least three conclusions can be drawn from this study:

Firstly protocol A is equally effective as protocol B. Secondly; it appears that combining aminoglycoside with Ceftriaxone therapeutically has no (P=0.09) significant benefit over Ceftriaxone alone. Finally protocol B is less expensive in terms of total therapy than protocol A and can be used without fear even in subnormal functioning kidney.

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