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Research Article

The Efficacy and Safety of Single Daily Dosing Ceftriaxone and Metronidazole vs the Triple Antibiotic Regimen for Complicated Appendicitis in Children

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Abstract

Triple antibiotic therapy using ampicillin, gentamicin, and metronidazole (AGM) providing broad-spectrum coverage of gram-positive, gram-negative, and anaerobic bacteria, has been the standard treatment of complicated appendicitis in children.

Keywords: Ceftriaxone and Metronidazole; Safety; AGM; Appendicitis

Introduction

In our institute, ampicillin was given 4 times per day, metronidazole 3 times per day and gentamicin once daily. Gentamicin is an aminoglycoside with known renal and ototoxic side effects that requires serum levels measurement.

Administration of three antibiotics multiple times per day creating a complex dosing schedule which require the patient to be connected to the IV line most of the day, casing high incidence of IV line related infection, demand the treating nurses a lot of work that is time consuming and may increase the risk mistake in drug administration.

In 2006, St Peter., *et al*. showed that a 2-drug regimen consisting of ceftriaxone and metronidazole can be used in a single daily dosing regimen for perforated appendicitis with some clinical benefits including cost [1].

Based on the finding of this retrospective study, we started a definitive, prospective, randomized trial comparing single daily dosing with ceftriaxone and metronidazole (CM) to the standard triple antibiotic regimen of ampicillin, gentamicin, and metronidazole (AGM) that was the standard treatment at our institute.

All children diagnosed with complicated appendicitis on even day was treated with CM and those who diagnosed on odd day was treated with AGM.

Methods

A prospective randomized clinical study started after approval was obtained from H'aemek medical center internal review board (IRB). Patients were enrolled in the study only after obtaining consent from the patient's legal guardian. The consent forms and consent process were carefully evaluated by the IRB on a continual basis.

Participants

The study population consisted of children 14 years old or younger with complicated appendicitis. Inclusion criteria required the presence of perforation or periappendicular abscess that was ether operated or conservatively treated including those with an abscess identified by ultrasound (US) or computed tomography

(CT). These patients were included in the study because, at the time of this study, the standard management in our institution for children with complicated appendicitis was conservative treatment followed by interval appendectomy. Exclusion criteria included patients with a documented allergy to any of the medications in the trial or patient with renal insufficiency that could not be treated with gentamicin.

Interventions

After determination of complicated appendicitis, patients were randomized to receive ceftriaxone and metronidazole (CM) or the triple antibiotic ampicillin, gentamicin, and metronidazole (AGM) based on the day of admission. Children who were diagnosed of having complicated appendicitis on an even day started an IV AGM antibiotic treatment and children diagnosed on an odd day started an IV CM antibiotic treatment.

Sample size

The power calculation was based on the number of patient treated for complicated appendicitis in our institute previously. A sample size of 30 patients in each arm with α of .05 provided a power of 0.82.

Assignment

Complicated appendicitis was diagnosed based on clinical, laboratory and radiologic parameters for patients treated conservatively and on the operating finding, by the surgeon, for patient that were operated.

Protocol

When a patient were diagnosed with complicate appendicitis we started a conservative treatment that include NPO, intravenous (IV) hydration with 1/3 saline and glucose 5%, pain control and IV antibiotic. The group allotted to the 2-drug regimen received once a-day dosing of Ceftriaxone 50 mg/kg and Metronidazole 30 mg/kg. The group randomized to the 3-drug regimen received Ampicillin 25 mg/kg per dose every 6 hours, metronidazole 10mg/kg per dose every 8 hours, and Gentamicin 5mg/kg once a day. In this group, serum Gentamicin peak and trough levels were drawn before the fourth dose.

In patient with perforate appendicitis that wasn't diagnosed before the operation, appendectomies were performed by one of the 4 constitutional staff surgeons as dictated by the call schedule. A white blood cell count, renal function and liver function test were taken before starting the antibiotic treatment and repeated on day 4 in all patients. Abdominal US and CT scans were obtained as clinically necessary to make the diagnosis of appendicitis. Nasogastric tubes were not used after the operation. Postoperative orders were controlled via a standard order set for all operations.

On the fifth treating day, if the white blood cell count was normal, the patient was not febrile, and was tolerating a regular diet, they were discharged home without oral antibiotics. If the patient was febrile and leukocytosis was found, the antibiotic treatment continued and an abdominal US was obtained to evaluate for the presence of an abscess.

In addition, US or CT scans were obtained if the patient's clinical condition suggested an abdominal abscess at any time after 7 days and the a white blood cell count evaluation is repeated. All patients who developed abscesses were treated with IV antibiotics consisting of the original regimen or changed to Tazocin based on the clinical situation and blood culture test. Drainage and length of treatment of abscesses were dictated by the treating surgeons.

Data collection

Data were collected prospectively. At the time of presentation, the patient's age, weight, sex, days of symptoms, maximum temperature, white blood cell count and renal function and liver function test were collected.

The outcome variables included maximum daily temperatures for each of the first 12 postoperative days, time to initial oral intake, length of hospitalization, length of antibiotic therapy, abscess rate, wound infection rate, and any abnormal findings during the follow-up visits.

Statistical analysis

The difference between the 2 treatment groups were assessed by χ^2 tests or Fisher exact tests where appropriate for categorical data and 2 independent sample t test or the Mann Whitney test where appropriate for continuous data. Significance was defined as P value ≤.05. Descriptive statistics were calculated as mean ± SD.

Results

From July 2008 to June 2009, 43 children with complicated appendicitis were enrolled in the study and no one was dropped from the study.

Demographic and clinical presentation data

There were no statistically significant differences in demographic data except that a larger percentage of male patients received the AGM treatment than the CM treatment 10 (45.5%) and 19 (90.5%) patient respectively (p<.002) (Table 1). The only statistically significant differences regarding anamnesis data was a longer history of abdominal pain for the children in the CM group than in the AGM group, 3.7 ± 1.6 days and 2.4 ± 1.1 days respectively (P<0.005). There were no statistically significant differences in all the physical examination parameter between the groups (Table 1).

Data	CM (n=22)	AGM (n=21)	p
Demography			
Age	7.1 ± 3.0	6.8 ± 3.6	.76
Males (%)	10 (45.5%)	19 (90.5%)	.002
History			
Abdominal pain n (%)	22 (100%)	21(100%)	1.00
Days	3.7 ± 1.6	2.4 ± 1.1	.005
Pain RLQ	8 (42.1%)	9 (52.9%)	.52
Vomiting (%)	18 (81.8%)	19 (90.5%)	.66
Diarrhea (%)[1]	9 (47.4%)	6 (33.3%)	.39
Physical examination			
Tenderness	21 (95.5%)	21 (100%)	1.00
RLQ Tenderness	9 (45%)	13 (61.9%)	.28
Peritonitis	16 (72.7%)	13 (61.9%)	.76
Mass	2 (11.8%)	1 (6.7%)	

Table 1: Demographic and clinical presentation data.

Laboratory and radiologic data

Laboratory tests were not statistically significantly different upon admission and did not differ after 4 days of treatment (Table 2). There were no statistically significant differences in the leukocyte count between the CM and AGM groups which was 19.33 ± 7.79 and 18.53 ± 4.33 on admission and decline to 13.06 ± 5.85 and 11.66 ± 4.48 respectively after 4 days (Figure 2). The Neutrophile percent show the same profile as the leukocyte (Figure 3). There was a statistically significant difference in preoperative radiologic finding. Free fluid on AUS was found in 17 (81.0%) of the AGM group and 8 (40.0%) of the CM (p<0.007) and abdominal abscess was found in 11 (55.0%) of the CM group and only 1 (4.8%) of the AGM (p<.001).

Clinical outcome

There were no statistically significant differences in the clinical outcomes between the groups. The maximum daily temperature was not statistically significant different between the 2 groups (figure 1).

Data	CM (N=22)	AGM (N=21)	p
WBC Admission	19.33 ± 7.79	18.53 ± 4.33	.68
Day 4	13.06 ± 5.85	11.66 ± 4.48	.42
Seg Admission	83.18 ± 7.05	85.49 ± 5.43	.25
Day 4	69.58 ± 16.61	69.86 ± 8.84	.95
Radiology finding			
Normal	1 (5.0%)	1 (4.8%)	1.00
Fecolith	3 (15.0%)	8 (38.1%)	.10
Free Fluid	8 (40.0%)	17 (81.0%)	.007
Abscess	11 (55.0%)	1 (4.8%)	.001

Table 2: Laboratory and radiology results.

There was no statistically significant difference in the length of hospital stay (median CM: 10.5 vs. AGM: 11.0 days) and there were no statistically significant differences in all early and late complications between the groups (Table 3).

Parameter	CM (n=22)	AGM (n=21)	p
IV n (%)	22 (100%)	21 (100%)	
Days (median)	5.8 ± 4.6 (5)	7.1 ± 3.5 (7)	.31
NGT n (%)	8 (36.4)	8 (40.0)	.81
Days (median)	5.1 ± 2.8 (4)	4.6 ± 2.2 (4)	.68
MO n (%)	9 (45.0%)	13 (61.9%)	.28
Days (median)	3.1 ± 3.0 (2)	2.3 ± 1.2 (2)	1.00*
NPO n (%)	19(90.5%)	21 (100%)	.49
Days (median)	4.6 ± 4.8 (2)	3.8 ± 2.9 (3)	.89*
Antibiotic days	7.4 ± 2.4	8.4 ± 3.1	.30
(median, range)	(8; 2-12)	(8; 4-15)	
LOS days	12.6 ± 8.1	11.5 ± 4.2	.58*
(median, range)	(10.5; 3-35)	(11.0; 4-21)	
Early complications			
Abdominal abscess	7 (33.3%)	11 (52.4%)	.21
Drainage	7 (33.3%)	8 (38.1%)	.75
Ileus	3 (14.3%)	2 (9.5%)	1.00
Metallic taste	1 (4.8%)	0 (0.0%)	1.00
Death	0 (0.0%)	0 (0.0%)	
None	12 (57.1%)	9 (42.9%)	.36
Long term complications	N=18	N=15	
Abdominal pain	1 (5.9%)	3 (20.0%)	.32
Readmissions	2 (11.1%)	4 (26.7%)	.38
Death	0 (0.0%)	0 (0.0%)	
None	16 (88.9%)	11 (73.3%)	.38

Table 3: Clinical Outcomes.

*Mann Whitney test.

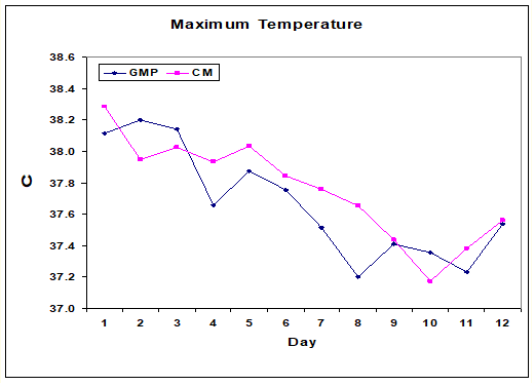

Figure 1: Maximum recorded temperature for the 2 groups on admission and each of the first 12 postoperative days.

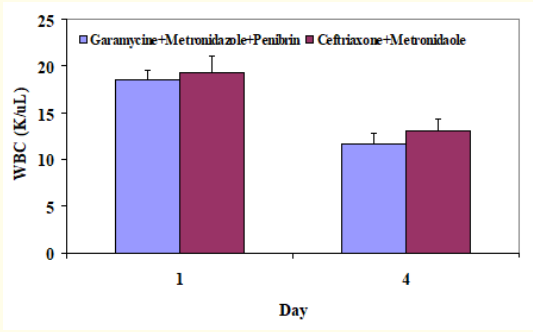

Figure 2: WBC by group.
(Bars are standard error of the mean).

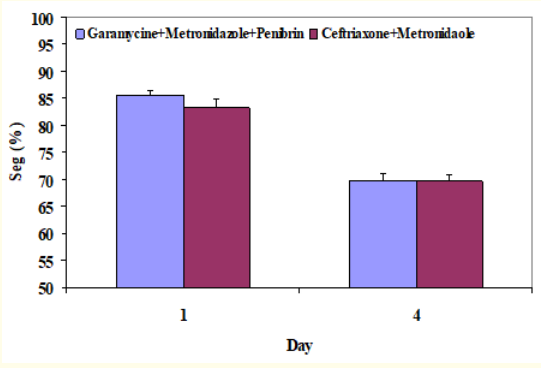

Figure 3: Segment (%) by group.
(Bars are standard error of the mean).

Discussion

A single daily dosing of antibiotic for treatment of complicated appendicitis have some important clinical benefits including simple dosing schedule that can reduce a lot of work from the treating nurses and may decrease the risk of mistake in drug administration, demand the patient be connected to the IV line for short time only once a day instead of most of the day for the triple antibiotics, cause less IV line infection and may cost less.

On behalf of all these advantages and despite several reports of simpler antibiotic regimens [3-5], the triple antibiotic therapy for complicated appendicitis is still the most common practice in pediatric surgeon.

Monotherapy with newer broad-spectrum agents such as piperacillin/tazobactam for intraabdominal infections has recently been shown to be equally efficacious as traditional triple therapy [3,4]. Similarly, cefotaxime, a cephalosporin with a similar profile to ceftriaxone, has been shown to be equal to the aforementioned monotherapy schedule of piperacillin/tazobactam in children with complicated perforated appendicitis when combined with metronidazole [5]. It has been shown that ceftriaxone and metronidazole provide comprehensive coverage for most enteric organisms in prophylactic studies as well as traumatic and surgical contamination studies [6]. However, the novel contribution of the regimen used in our study is the institution of once-a-day dosing of metronidazole. Previously, once daily dosing of ceftriaxone and metronidazole has been shown to be superior to ampicillin, netilmicin, and metronidazole for the treatment of bacterial peritonitis in a prospective, controlled clinical trial in adults [7-15].

A retrospective study that showed that a 2-drug regimen consisting of ceftriaxone (Rocephin, Roche Pharmaceuticals, Nutley, NJ) and metronidazole (Flagyl) has the efficacy same and may be more safety from the triple antibiotic treatment with ampicillin, gentamycin and cilindamyn for treating children with perforate appendicitis was published by St Peter., *et al*. [1]. They suggest that a prospective study may insure the results confirm that single daily dosing regimen may be used for children with perforated appendicitis. Based on the finding of this retrospective study, we started a definitive, prospective, randomized trial comparing single daily dosing with ceftriaxone and metronidazole (CM) to the standard

triple antibiotic regimen of ampicillin, gentamicin, and metronidazole (AGM) that was the standard treatment at our institute.

In 2008, Peter., *et al*. published a new prospective study that showed that single daily dosing of ceftriaxone and metronidazole (CM) has the same safety and efficacy as the standard triple antibiotic regimen of ampicillin, gentamicin, and clindamycin. Regarding charges, they found the CM regimen to be significantly more cost-effective. The additional antibiotic charges for the patients who developed an abscess were, on average, $8000 less in the CM group.

In our study a larger percentage of male patients received the AGM treatment than the CM drug treatment, 19 (90.5%) vs. 10 (45.5%) (p<.002). This difference did not found to influence on the treatment outcome. The CM group had more days with abdominal pain 3.7 ± 1.6 vs. 2.4 ± 1.1 (p<.005) prior to admission. This is an unusual but possible event in a prospective randomized trial even when the randomization process was strictly followed with no mistakes in the order. Radiology findings include AUS or ACT differed between the 2 groups with a larger percentage of patients in the AGM group were found on admission with abdominal free fluid (81.0% vs. 40.0%, p<.007) and a larger percentage of patients in the CM group were found with an abscess (55.0% vs. 4.8%, p<.001). This difference is probably related to the more days with abdominal pain in the CM group. We would expect these finding that may indicate a more progress inflammatory processes to influence on the clinical outcome in a way that the CM group may need more days on IV, NPO, antibiotic or hospitalization, but there was no difference in all the clinical outcome and there was no difference not in the early complication nor in the late complication as well.

Conclusion

Our results showed that a single daily dosing of ceftriaxone and metronidazole antibiotic treatment has the same efficacy and safety as the triple antibiotic regimen for complicated appendicitis in children. Based on these results we recommend this treatment for children with complicate appendicitis.

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