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Evaluation of Serial C-Reactive Protein as a Predictor of Surgical Site Infection Following Emergency Laparotomy in Children in Ile-Ife, Nigeria

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Abstract

Background: Effective monitoring of patients post operatively may reduce morbidity and mortality in children undergoing emergency laparotomy and thus improve outcome. Early detection of complications post operatively is a very challenging task due to inadequate facilities for monitoring in our environment. C-Reactive Protein (CRP) may be used as an adjunct to clinical parameters for early detection of complications and prompt institution of treatment C-reactive protein is an effective, reliable, easy, fast and minimally invasive diagnostic modality for monitoring pediatric patients post operatively.

Objective: The aim of this study was to determine if serum CRP could predict surgical site infection in children who had emergency laparotomy.

Methodology: This was a prospective study carried out in the pediatric surgery Unit of the Obafemi Awolowo Teaching Hospitals Complex, Ile Ife, over a period of one year.

All patients presenting with acute abdominal condition requiring surgery at the children emergency room were recruited into the study after informed consent had been obtained from their parents or guardians. Following adequate resuscitation, blood sample was collected to measure the preoperative CRP level. Post operatively, serial blood samples were collected at 24 h interval over a six day period for CRP estimation using ELISA method. Six hourly vital signs (Blood pressure, pulse rate, temperature, and respiratory rate) together with daily abdominal examination were done for 6 days post operatively to detect surgical site infection. Abdominopelvic ultrasound was done on days 4 and 6 to rule out intra-abdominal collection.

Demographic, clinical and measured CRP levels were entered into a proforma and analyzed using SPSS software version 22 (SPSS Inc, Chicago, Illinois).

A criterion of $P<0.05$ was used to determine statistical significance.

Results: Thirty seven patients were recruited for the study with a mean age of 9.06 ± years and age range of 6 months to 15 years. There were 24 males (64.8%) and 13 females (35.2%).

The mean preoperative level of serum CRP was 122.65 ± 88.1 mg/L (normal value: <3 mg/L) Thirteen (35.1%) patients had surgical site infection.

The mean serum CRP of the patients with normal postoperative course peaked at 48 h post-surgery and then steadily declined. The patients who developed surgical site infection had an accelerated rise in mean serum CRP post operatively compared to the patients without surgical site infection. Their serum CRP continued to rise up to 144 hours post-surgery. The result also showed that elevation of mean serum CRP in those who developed surgical site infection predated the earliest change in their clinical signs by 12 h.

Conclusion: The study showed that the mean preoperative CRP level is elevated above the normal range in children undergoing emergency laparotomy in OAUTHC Ile Ife. The mean serum CRP continues to rise and peaks at 48 h after surgery and then maintains a downward trend in patients with normal post-operative course while for patients with surgical site infection, it still maintains an upward trend 48 h after surgery. Serum CRP identified those who develop surgical site infections by 3rd post-operative day.

Keywords: C-reactive protein; Postoperative monitoring; Surgical site infection

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Introduction

Acute abdominal conditions requiring surgery are common pediatric surgical emergencies. Emergency laparotomy carries considerable risk of mortality and infective postoperative complications [1]. Effective monitoring postoperatively may reduce mortality and morbidity in children undergoing emergency laparotomy and thus improve outcome. Emergency conditions contribute considerably to the number of patients (up to 30% to 40%) admitted to surgical departments in poor resource countries [2]. These acute emergencies are associated with high rates of infective complications, significant costs for the surgical departments and considerably high (almost 90% of deaths) mortality occurring within 48 h of admissions [2]. In Zaria, the infection rate following emergency procedures was found to be about 25.8% [3].

Monitoring of these patients post operatively have also become a very challenging task due to decreasing number of trained staff, and increasing patient load. Clinical findings still remain the main modality of patient evaluation due to lack of facilities for adequate monitoring of patients in these region. Because of these challenges, diagnosis of postoperative infective complications is often suggested by changes in the clinical signs such as the pulse rate, temperature, respiratory rate and abdominal examination findings and by the time these signs are apparent, the patients are already critically ill [4,5]. This increases morbidity and mortality in these patients [6]. If there were an appropriate marker, postoperative infective complications could be diagnosed earlier. An early and reliable diagnosis, together with a prompt and adequate treatment including immediate surgical repair of the underlying abdominal pathology will significantly reduce the morbidity and mortality associated with this condition. There is therefore a need for an effective, reliable, easy, fast and minimally invasive diagnostic modality for monitoring pediatric surgical patients during postoperative course.

C-Reactive Protein (CRP) is an acute phase protein which may be used for this purpose. Acute-phase proteins are proteins whose plasma concentration increases (positive acute-phase proteins) by at least 25% during inflammatory disorders [7]. The magnitude of their increase varies from about 50% in the case of ceruloplasmin and several complement components to as much as 1000-fold in the case of C-reactive protein and serum Amyloid A [7]. CRP production is part of the nonspecific acute-phase response to most forms of inflammation, infection, and tissue damage. Because of this ability, CRP serum concentration can be assayed in pediatric patients postoperatively to establish a trend in its value. Studies have shown that changes in serum CRP did not only detect presence of surgical site infection but also predate changes in clinical parameters. This may make serial CRP measurement a safe tool in monitoring children after emergency laparotomy. Deviation from the normal pattern may suggest surgical site infection thereby leading to early prediction and identification of surgical site infection in these children. The aim of this study was therefore to evaluate the reliability of serum CRP as a predictor of surgical site infection following emergency laparotomy in children in Ile-Ife, Nigeria.

Methodology

This was a prospective study carried out in the Pediatric Surgery Unit of the Obafemi Awolowo Teaching Hospitals Complex, Ile Ife, from March 2017 to December 2017. Ethical approval was obtained from the hospital's ethics and research committee.

Table 1: Socio-demographic characteristics of the study participants.

Variable	Over All Distribution (N=37)
*Age Group:	
6 Months to <2 Years	4 (10.8%)
2 Years - 5 Years	1 (2.7%)
6 Years - 10 Years	18 (48.6%)
11 Years - 15 Years	14 (37.8%)
Mean Age (Years)	9.06 ± 3.8
Sex:	
Male	24 (64.8%)
Female	13 (34.2%)

Table 2: Showing the different distribution of diagnosis.

Diagnosis	Frequency (%)
Ruptured appendicitis	13 (35.1%)
Typhoid perforation	8 (21.6%)
Acute uncomplicated appendicitis	7 (18.9%)
Intussusception	3 (8.1%)
Small bowel volvulus	2 (5.4%)
Infected mesenteric cyst	1 (2.7%)
Intussusception with peritonitis	1 (2.7%)
Splenic trauma with peritonitis	1 (2.7%)
Enterocutanous fistula with peritonitis	1 (2.7%)

All eligible patients presenting with acute abdominal condition requiring surgery at the children emergency room were fully resuscitated with intravenous infusion of 4.3% dextrose in 1/5 saline, broad spectrum parenteral antibiotics, and nil per os, Nasogstric tube as well as urinary catheter were inserted. Blood samples were collected for full blood count and chemistry. They were recruited for the study after an informed consent was obtained from the parents or guardians. Demographic and clinical data were obtained based on the proforma designed for the study. After evaluation, before surgery 3 ml to 5 ml of blood was collected in a plain bottle and allowed to coagulate after which it was centrifuged and the serum decanted and stored at -70°C until analyzed.

Intraoperatively, a broad-spectrum antibiotic based on unit protocol was given at induction of anesthesia. Under general anesthesia, skin preparation with antiseptic solution was done followed by draping; peritoneal access was gained using appropriate incision based on the underlying pathology. Other steps of the procedure depended on the pathology. For patients with peritonitis, the peritoneal cavity was copiously irrigated with normal saline, then mopped dry. Primary closure was done for all wounds.

Postoperatively, parenteral antibiotics was continued until oral intake was established after which they were converted to oral. Serial blood samples (3 ml to 5 ml) were collected 24-hourly till a total of six samples was collected and the process repeated. Vital signs which included pulse rate, respiratory rate, temperature, blood pressure were recorded 6-hourly and daily abdominal examination done till the patient was discharged, looking out for signs of surgical site. For the purpose of the study, surgical site infection was defined using the centre for disease control criteria (Appendix 2).

Abdominopelvic ultrasound scan was done for all the patients

Table 3: 24 Hourly mean CRP measurement in the patients with or without surgical site infections.

Time	Complication	CRP Value(mg/dl)	P Value	Remark
Pre op CRP	No	119.33 ± 87.9	7.63	Not Significant
	Yes	128.8 ± 91.6		
CRP 24 hours post-surgery	No	124.23 ± 53.2	0.001	Significant
	Yes	163.48 ± 41.4		
CRP 48 hours post-surgery	No	132.59 ± 78.1	0.04	Significant
	Yes	170.44 ± 42.9		
CRP 72 hours post-surgery	No	122.42 ± 73.1	0.03	Significant
	Yes	183.80 ± 42.5		
CRP 96 hours post-surgery	No	112.75 ± 79.1	0	Significant
	Yes	196.69 ± 12.7		
CRP120 hours post-surgery	No	103.84 ± 62.7	0	Significant
	Yes	220.00 ± 34.4		
CRP 144 hours post-surgery	No	89.12 ± 50.5	0	Significant
	Yes	251.30 ± 46.7		

on postoperative days 4 and 6 in order to exclude or identify intra-abdominal septic collections.

Intra-abdominal septic collection was considered positive if ultrasound showed fluid collection with low or medium level mobile echoes within the peritoneal cavity. Mindray diagnostic ultrasound system model DC-7 produced by Shenzehn Mindray Bio-medical Electronics Co., Ltd. was used for the study.

For those with incisional surgical site infection, the management included removal of alternate skin sutures and daily dressing with honey. Where necessary, secondary wound closure was done after the infection was controlled and wound well granulated. For patients with peritoneal collections, laparotomy and drainage of collection was done. Patients were discharged when fit and then followed up in the clinic until postoperative day 30. The clinical information was entered in the proforma designed for the study.

Samples were pooled and analyzed in batches by the chemical pathologist.

The serum CRP assay was done using the High-sensitivity C Reactive Protein (hsCRP) Enzyme Linked Immunosorbent Assay (ELISA) kits produced by Monobind Inc., Lake Forest, CA 52630, USA.

Procedure for hsCRP ELISA assay:

Before proceeding with the assay, all reagents, serum references and controls were brought to room temperature (20 to 27°C). Step involved were:

1. Formatting of the microplates' wells for each serum reference, control and patient specimen to be assayed in duplicate; replacing any unused micro well strips back into the aluminum bag, seal and store at 2°C to 8°C.

2. Pipetting of 0.025 ml (25 µl) of the appropriate serum reference, diluted specimen or control (Patient Sample Preparation) into the assigned wells.

3. Addition of 0.100 ml (100 µl) of the CRP Tracer Reagent to each well.

4. Swirling the microplate gently for 20 sec to 30 sec to mix and cover.

5. Incubation for 15 min at room temperature.

6. Discarding the contents of the microplate by decantation or aspiration. If decanting, tapping and blotting the plate dry with absorbent paper.

7. Addition of 350 µl of wash buffer, decanting (with tapping and blotting) or aspirate. Repetition of four (4) additional times for a total of five (5) washes.

8. Addition of 0.100 ml (100 µl) of Working Signal Reagent to all wells.

9. Incubation at room temperature for 5 minutes in the dark.

10. Reading of the Relative Light Units (RLU) in each well using a microplate luminometer. The results shall be read within thirty (30) minutes of adding the working signal reagent, using a wavelength of 450 nm in a microplate reader with a background wavelength of 620 nm to 650 nm to minimize well imperfections.

The above procedure was done by the chemical pathologist data was analyzed using the Statistical Package for Social Sciences version 22 (SPSS Inc. Chicago, Illinois). The mean and standard deviation were calculated for numerical continuous variables (age, pulse rate, respiratory rate, temperature, blood pressure, CRP values) while the discrete variables (sex, diagnosis, complications) were recorded in percentages.

The CRP trend of those who had normal post-operative course was compared with that of those who developed surgical site infection to ascertain if there was a difference between them and also identify at what point the difference occurred. The student t test was used to test for significance in the serial CRP value between the two groups. A criterion of $P<0.05$ was used to determine significance.

Results

During the study period, thirty seven patients were recruited. The age range of the patients was 6 months to 15 years with a mean age 9.06 ± 3.8 years. There were 24 males (64.8%) and 13 females (35.2%).

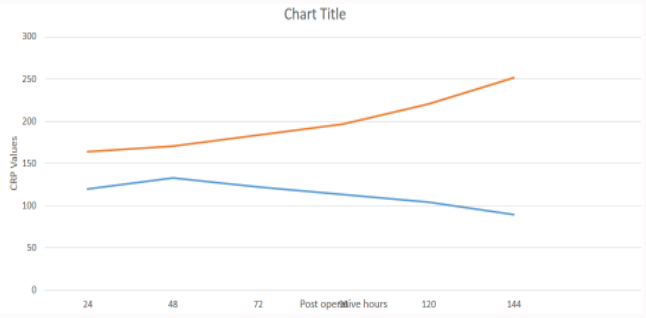

Figure 1: Pattern of mean CRP changes in the patients with or without surgical site infections.
Blue line: Normal postoperative course; Red line: Surgical site infection

Figure 2: Mean temperature pattern of the patients with or without surgical site infections.
Blue line: Normal postoperative course; Red line: Surgical site infection

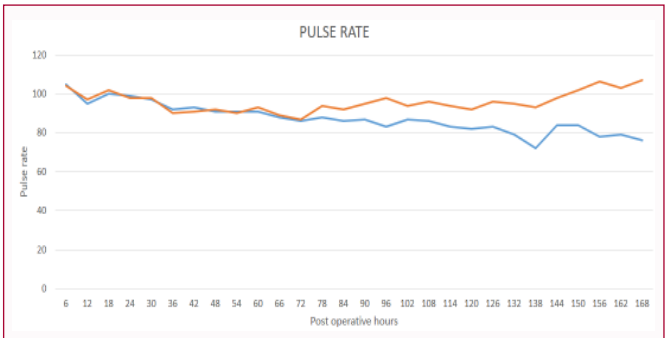

Figure 3: Mean pulse rate pattern in the patients with or without surgical site infection.
Blue line: Normal postoperative course; Red line: Surgical site infection

The most common age group was 6 years to 10 years and it accounted for 48.6% (n=18) as shown in Table 1.

Ruptured appendicitis accounted for majority of the diagnosis 13 (35.1%), this was followed by typhoid perforation 8 (21.6%) (Table 2).

The mean preoperative level of serum CRP was 122.65 mg/L ± 88.1 (normal value <3 mg/l). Thirteen (35.1%) patients had surgical site infection while the remaining 24 (64.9%) patients had a normal postoperative course.

The preoperative mean serum CRP of those who had normal postoperative course was 119.3 ± 87.9 while that of those who later developed surgical site infection was 128.8 ± 91.6 (p=7.60) Table 3.

The mean serum CRP of the patients with normal postoperative course peaked at 48 h post- surgery and then steadily declined falling below the preoperative level by 144 h.

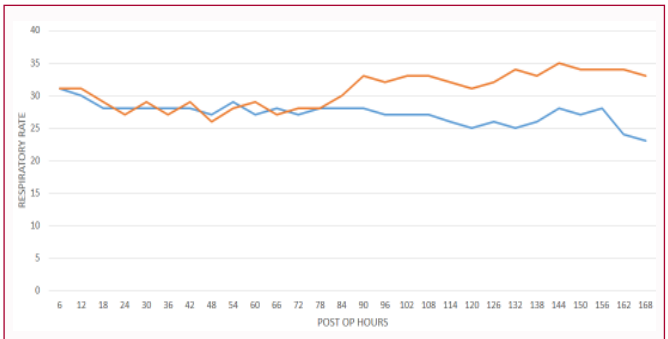

Figure 4: Mean respiratory rate pattern in the two groups.
Blue line: Normal postoperative course; Red line: Surgical site infection

Figure 5: Pattern of changes in the mean CRP and mean temperature in those with surgical site infection.
Red line: Temperature pattern; Blue line: CRP pattern

Though it did not fall to the normal level. The patients who developed surgical site infection had an accelerated rise in mean serum CRP post operatively compared to the patients without surgical site infection. Their serum CRP continued to rise up to 144-h post-surgery (Figure 1).

The post-operative mean serums CRP are as shown in Table 3. There was a statistical significant difference in the serum CRP between those who had complications and those with normal outcome, $p<0.05$.

A persistent rise in the mean temperature was noticed in the group with surgical site infection from 60 h after surgery. The temperature rose beyond normal limit by 96 h. The mean temperature of the patients with normal post-operative course was within normal range during this period (Figure 2).

There was no appreciable difference in the pattern of mean pulse rate of the patients with normal post-operative course compared with that of the patients with surgical site infection until after 72 h. The mean pulse rate of the patients with surgical site infection increased after 72 h while that of the normal patients maintained a downward course but within normal limit (Figure 3).

The change in the mean respiratory rate in the patients with surgical site infection became apparent after 84 h. Their mean respiratory rate increased after 84 h unlike that of the patients with normal post-operative course (Figure 4).

The mean systolic and diastolic blood pressure of the patients with surgical site infection and those with normal post-operative course had a similar pattern throughout the study period. They both maintained a normal range of 100 to 110 mmHg for systolic and 60 to 70 mmHg for the diastolic pressure.

Surgical site infection

Increasing temperature was the earliest clinical manifestation of

surgical site infection and it was noticed at 60 h after surgery.

The graph shows that there was an early increase in the mean CRP value compared to the mean temperature among the patients with surgical site infection. The increase in CRP preceded the increase in temperature by 12 h (Figure 5).

Discussion

The study showed that the mean preoperative level of CRP in children undergoing emergency laparotomy was 122.66 ± 88.1 mg/L (27.7 to 205.9 mg/l). This result is comparable to the finding of Chana et al. [8] who found a mean preoperative level of 86.4 mg/L among children with peritonitis undergoing emergency surgery in Aligarh, India. All of them had elevation in the mean preoperative serum CRP although the value was higher in my study. The higher level obtained in this study may be because of high levels of inflammatory response aggravated by late presentation due to low socio economic status [9-11]. This increases the severity of inflammatory response and thus CRP production. Most of our patients presented with ruptured appendicitis and typhoid perforation.

The mean serum CRP value of patients that had a normal postoperative recovery peaked at 48 h post operatively at a mean value of 132.6 mg/L ± 78.6 and then maintained a downward trend afterwards to a mean value of 89.1 mg/L ± 50.5 on post-operative day 6. Straatman et al. [9] found similar pattern in adult patients who underwent emergency colorectal surgery. They observed a peak of 243 mg/L at post-operative day two and then a gradual fall subsequently, achieving a value of 82.86 mg/L on the seventh postoperative day [9]. This suggests that the pattern of mean CRP changes in pediatric patients is similar to that of adult patients after emergency laparotomy.

The patients with surgical site infection had mean postoperative CRP values that were consistently higher than that of the patients with normal postoperative course all through the duration of the study. Their CRP value maintained an upward trend from 1st post-operative day to the 6th post-operative day compared to those without complications whose mean CRP levels decline after 48 h. This suggests that CRP estimation could be used to predict patients at risk of developing post-operative surgical site infection. This in turn would enable early investigation and prompt institution of therapy so as to reduce morbidity and mortality. This is similar to the findings of Woeste et al. [12], who observed that prolonged elevation and a missing decline in CRP level preceded the occurrence of surgical site infection [8]. Pedersen et al. [13] also noted that post-operative CRP level was significantly higher in patients with septic complications than in patients without complications. Pederson et al. [13], Sara et al. [14] and Straatman et al. [15] observed that serum CRP may be used as a predictive tool for surgical site infection on the 3rd post-operative day. Sara et al. [14] established a cut off of 159 mg/L (range 92 to 200) for post-operative day 3 and 114 mg/L (48 to 158) for post-operative day 5 while Pederson et al. [13] noted a cut off of 200 mg/l. Straatman et al. [16] proposed a level of 140 mg/L as cut off for PODs 3, 4 and 5 as a marker for surgical site infection in patients who underwent major abdominal surgery. In our study we found a mean value of 183.5 mg/L ± 42.5 on post-operative day 3 and 103.8 mg/L ± 62.8 on post-operative day 5 among those who had surgical site infection. However, and Woeste et al. [12] and Welsch et al. [17] noted that from the 4th postoperative day CRP levels significantly correlate with the changes in the clinical signs of patients after surgery.

Temperature change was the only clinical sign that suggested the presence of SSI in this cohort study. The temperature pattern began an upward trend at 60 h post-surgery compared to the patients with normal post-operative course. However, this rise in temperature pattern lags behind persistent elevation of CRP by 12 h. This suggests that serum CRP may predict surgical site infection earlier than routine clinical signs. This is in keeping with the findings of Povoa et al. [18] who noted that daily measurement of CRP is useful in the early detection of sepsis and it is more sensitive than routine markers, such as body temperature in detection of septic complications. The temperature of the patients with normal post-operative course was within normal range all through the duration of the study. This suggests that the initial rise in the CRP during the first 48 h after surgery was due to the effect of surgery.

Conclusion

The mean serum CRP continues to rise and peaks at 48 h after surgery and then maintains a downward trend in patients with normal post-operative course while for patients with surgical site infection, it still maintains an upward trend 48 h after surgery. Serial serum CRP measurement identified those who were likely to develop surgical site infections earlier than the clinical signs. Thus serum CRP measurement may be used in monitoring pediatric surgical patients post operatively after emergency laparotomy in our environment.

Recommendation

We recommend that serum CRP may be done as part of monitoring tool for patients with increased risk of developing surgical site infection after emergency laparotomy. Further studies may be needed using a larger sample to validate this findings in our environment.

Limitation

Patients with subclinical diseases that affect CRP that might have been missed.

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