

Role of serum C-reactive protein and interleukin-6 as a predictor of intra-abdominal and surgical site infections after elective abdominal surgery

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ABSTRACT

Introduction: Infections after surgeries considerably increase patients' hospital stay, thereby prolonging patients' early return to productive life. At the same time, the cost of hospitalization also increases. Therefore, if objective tests can predict infections before it actually happens, then more preventive measures in the form of upgrading antibiotics can be taken which might prevent patients from developing serious infections and thereby reduce morbidity and mortality of surgery. **Material and Methods:** It was a prospective cross sectional study to assess the efficacy of acute phase reactants C-reactive protein (CRP) and interleukin 6 (IL 6) in predicting infections in patients undergoing routine general surgical operations. A total of 74 patients were included in the study. Laparoscopic surgical procedures were not included in the study to maintain uniformity in the procedures. Data so collected were analyzed by using SPSS version 22. **Results:** A total of 27 patients developed wound infections postoperatively. The mean rise in the levels of CRP and IL 6 was higher in those patients who developed postoperative wound infections. The positive predictive value and negative predictive value was found to be better with IL 6 than with CRP. **Conclusion:** It may be concluded that a serial estimation of CRP and IL 6 postoperatively can predict infections and may be utilized routinely in general surgical practice.

Keywords: C- reactive protein, diagnostic accuracy, elective abdominal surgeries, interleukin 6, postoperative wound infections

Introduction

Infections at the surgical site are common after major abdominal surgeries. They have a bearing on the cost of hospitalization, morbidity, and outcome of the patients.^[1,2] Early clinical features resemble those of inflammation due to surgical trauma and hence unreliable to distinguish from the infective complications.^[3] In comparison, biological markers like C-reactive protein (CRP) are known to rise in the early postoperative period and normalize soon in patients with uneventful recovery.^[4,5] Interleukin 6 (IL 6)

is also known to predict surgical site infections after surgery.^[6,7] The present study was undertaken to assess the efficacy of CRP and IL 6 in predicting postoperative wound infections after undergoing elective major abdominal surgeries.

Material and Methods

The study was conducted in the Department of General Surgery, NEIGRIHMS Hospital, Shillong from March 2018 to February 2020. It was a prospective cross-sectional study to assess the diagnostic efficacy of CRP and IL 6 as a predictor of intra-abdominal or surgical site infections in patients undergoing non-emergency elective abdominal surgeries. For the purpose of uniformity in the cases, those patients undergoing laparoscopic

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Received: 18-06-2020

Revised: 08-09-2020

Accepted: 01-12-2020

Published: 30-01-2021

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_1191_20

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How to cite this article: Hajong R, Newme K, Nath CK, Moirangthem T, Dhal MR, Pala S. Role of serum C-reactive protein and interleukin-6 as a predictor of intra-abdominal and surgical site infections after elective abdominal surgery. J Family Med Prim Care 2021;10:403-6.

surgeries were excluded from the purview of the study. Only patients undergoing open elective surgeries were included in the study. Institute ethical clearance was obtained to conduct the study. Written informed consent was obtained from all the patients included in the study. Serum CRP and IL 6 were sent from the patients on post-operative days (PODs) 1, 2,3,5,7 and 10 days.

The CRP was estimated by immuno-rate method in Vitros 4600 microslide series (Make- Ortho-clinical Diagnostics, USA). Absorbance produced by sample was calculated based on the calibration curve stored using multilevel calibrator. Proper internal quality control was maintained by CRP performance verifier I and II (Make- Ortho-clinical Diagnostics, USA). Reference range was <10 mg/L.

IL-6 was estimated by chemi-luminescence method using Beckman coulter DXI immunoassay system (USA). Principle of the test was that IL-6 assay was a simultaneous one-step immune-enzymatic (“sandwich”) assay. Patient sample was added to a reaction vessel along with the paramagnetic particles coated with mouse monoclonal anti-human IL-6 and the alkaline phosphatase conjugate. After incubation in the reaction vessel, materials bound to the solid phase were held in a magnetic field, whereas unbound materials were washed away. Then, the chemiluminescent substrate Lumi-Phos 530 was added to the vessel and light generated by the reaction was measured with a lumino-meter. The light production was directly proportional to the concentration of IL-6 in the sample. The amount of IL = 6 in the sample was determined from a stored, multi-point calibration curve. Strict quality control was done by Biorad internal quality control. Reference range was 5.3–7.5 pg/ml.

Postoperatively patients’ wounds were opened on day 2 unless indicated otherwise and examined for any signs of infections. Wound swabs were sent from discharging wounds and antibiotics were given according to the sensitivity patterns. Data collected from the patients were analyzed using the SPSS version 22. Means of CRP and IL 6 were compared in patients with or without infection. Then cut off values were obtained for CRP and IL 6 from receiver operator characteristic (ROC) curve at acceptable sensitivity and specificity [Table 1]. Then positive predictive value (PPV) and negative predictive value (NPV) were calculated by Chi-square tests and by column and row method from SPSS. Ethical Approval was obtained from the ethics committee on 10th February 2018.

Results

A total of 74 patients were included in the study. And 42 males (56.8%) and 32 females (43.2%). 27 out of 74 (36.49%) patients developed postoperative infections. 24 patients had superficial wound infections and 3 patients had deep wound infections. No difference was found in the gender distribution of the patients with infections- 16 males and 11 females (*p* value - 0.81). The mean age of the patients was 41.01 ± 12.30 years with a median of 38.00. Post-operative

infections were detected mostly from day 3 to 5 as shown in Figure 1.

Mean hospital stay in patients without infection was much shorter (*p* – 0.001) as shown in Table 2, thereby leading to early return to normal activities.

The various types of surgeries that were included in the study are shown in Table 3. Three patients had deep surgical site infections involving muscles and beyond. *Escherichia coli* was the most common organism isolated and cultured from the wound swabs.

The mean rise in the levels of CRP and IL 6 was much higher in those patients who developed postoperative wound infections in comparison to those without infections [Table 4].

The PPV and the NPV of CRP were consistent with post-operative infections from day 5 after operations [Table 5]. In the case of IL

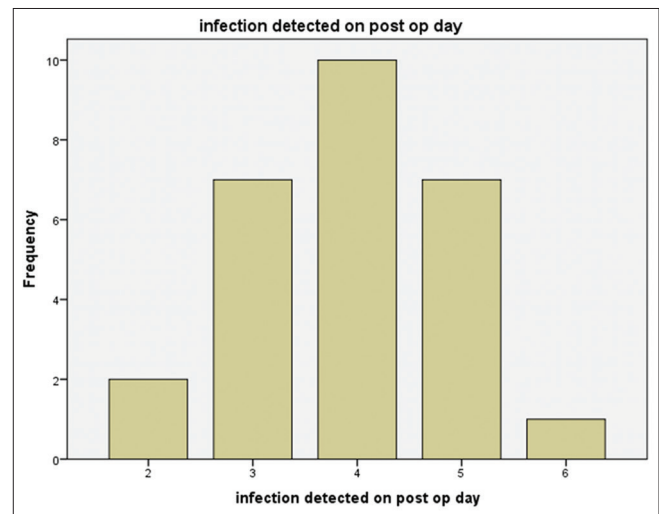


Figure 1: Showing day of infection detection

Table 1: Cut values for CRP and IL 6 from ROC curves at the given sensitivity and specificity

POD	Test	Cut off value	Sensitivity	Specificity
Day 1	CRP	6.75	74.10	59.60
	IL 6	6.00	88.90	84.80
Day 2	CRP	7.45	81.50	78.70
	IL 6	6.35	96.30	93.60
Day 3	CRP	7.75	96.30	76.60
	IL 6	6.85	96.30	100.00
Day 5	CRP	8.00	96.30	86.50
	IL 6	7.00	100.00	97.30
Day 7	CRP	7.80	100.00	75.00
	IL 6	6.50	100.00	83.30

Table 2: Length of hospital stay

Post-operative infection	Mean hospital stay	P
No	5.32±0.958	0.001
Yes	16.22±4.041	

Table 3: Types of operations, wound types and organisms

Type of operation	Nos (74)	Type of wound	No with infection (27)	Depth of infection	Type of organism
Open cholecystectomy	27	Clean	6	Superficial	<i>E. coli</i> -2, no growth-3, Klebsiella pneumoniae-1
Open CBD exploration	7	Clean contaminated	4	3 superficial, 1 deep	<i>E. coli</i> -2, MRSA-1, Acinetobacter baumannii-1
Right hemicolectomy	7	Contaminated	4	3 superficial, 1 deep	<i>E. coli</i> -2, no growth-1, Acinetobacter baumannii-1
TV & GJA	5	Clean contaminated	2	2 superficial	Klebsiella pneumoniae-1, pseudomonas aeruginosa-1
Distal gastrectomy	3	Clean contaminated	1	Superficial	<i>E. coli</i>
Left colectomy	2	Contaminated	1	Superficial	<i>E. coli</i>
APR	2	Contaminated	1	Superficial	Acinetobacter baumannii
Splenectomy	4	Clean	2	Superficial	No growth
Right extended hepatectomy	1	Clean contaminated	1	Deep	<i>E. coli</i>
Excision of biliary cystadenoma	1	Clean contaminated	0		
Hepatic hydatid cyst excision	3	Clean	1	Superficial	<i>E. coli</i>
Excision of choledochal cyst	2	Clean contaminated	1	Superficial	<i>E. coli</i>
Whipples' operation	7	Clean contaminated	2	2 superficial	No growth-1, <i>E. coli</i> -1
Radical cholecystectomy	3	Clean contaminated	1	Superficial	<i>E. coli</i>

Table 4: Comparison of mean CRP and IL 6 with and without infection

Parameter	Infection	POD 1	POD 2	POD 3	POD 5	POD 7
CRP	No	6.321 (1.287)	6.711 (1.072)	6.951 (0.974)	6.908 (1.092)	7.050 (1.136)
	Yes	7.537 (1.132)	8.370 (1.140)	10.067 (1.770)	12.119 (1.923)	12.600 (2.087)
IL 6	No	5.760 (0.249)	5.894 (0.352)	6.068 (0.480)	6.046 (0.404)	6.000 (0.447)
	Yes	6.400 (0.395)	6.989 (0.333)	7.622 (0.364)	8.200 (0.331)	8.337 (.633)

Table 5: PPV and NPV of CRP and IL 6 postoperatively

POD	Parameter	Sensitivity	Specificity	PPV	NPV	P
Day 1	CRP	74.10	59.60	51.30	80.00	0.005
	IL 6	88.90	84.80	77.40	92.90	0.001
Day 2	CRP	81.50	78.70	68.80	88.10	0.001
	IL 6	96.30	93.60	89.70	97.80	0.001
Day 3	CRP3	96.30	76.60	70.30	97.30	0.001
	IL 6	96.30	100.00	100.00	97.9	0.001
Day 5	CRP	96.30	86.50	83.90	97.00	0.001
	IL 6	100.00	97.30	96.40	100.00	0.001
Day 7	CRP	100.00	75.00	96.40	100.00	0.001
	IL 6	100.00	83.30	96.40	100.00	0.001

6, PPV and NPV were consistent with post-operative infections from second day.

Discussion

CRP is a biological marker for inflammation with a stable decay rate. Its level increases during bacterial infections in response to certain monocytic mediators like IL-1 and IL-6.^[8,9] IL-6 induces the CRP gene during inflammation^[10] and a correlation has been observed between the increasing levels of IL-6 and CRP during inflammation.^[11]

IL 6 is a pleiotropic cytokine with varied functions. It is an integral mediator of physiological acute phase response to trauma. It also modulates proliferation, maturation of hematopoietic progenitors and other cell lineages, and regulates growth of

cancer cell lines and certain metabolic activities. The role of IL 6 after elective operations, burns and trauma has been studied recently. Prolonged and excessive elevations of serum IL 6 levels after trauma or surgery are associated with increased morbidity and mortality.^[7,12]

Gans *et al.*^[13] have opined that in patients with CRP below 159 mg/L (Range- 52-200) on the third POD with a NPV of 90% had very low probability of suffering from post-operative infections and they could be discharged safely early. Singh *et al.*^[14] also opined that a CRP value of 172 mg/L on 3rd POD was associated with lesser post-operative complications. In the present study also, it was seen that those patients who did not have post-operative wound complications had a mean CRP of 6.951 (range: 5.9744–7.9254 mg/L) on the third POD in contrast to 10.067 in those patients with post-operative infections with a NPV of 97.30% and were discharged early.

Gans *et al.*^[13] in their meta-analysis have found that the pooled sensitivity of 86% (95% CI 79–91%), and specificity of 86% (95% CI 75–92%), for CRP were higher for POD 5 than other PODs ($p < 0.001$). The pooled PPV in their series ranged from 41% on POD 1 to 64% on POD 5. The pooled NPV in their series ranged from 82% on POD 1 to 92% on POD 5. In the present study, sensitivity 96.30% and a specificity of 86.50% were noted on POD 5. The PPV ranged from 51.30% on POD 1 to 83.90% on POD 5. The NPV ranged from 80% on POD 1 to 97% on POD 5 in the present series.

Fujii *et al.*^[15] in their series concluded that elevated serum CRP levels correlated well with incisional surgical site infections and persistent elevation of CRP was predictive of incisional surgical site infections provided pneumonia or anastomotic leakage were excluded. In the present series, it was found that serum CRP levels correlated well with postoperative wound infections at the surgical sites and patients with lower levels of CRP levels postoperatively were discharged much earlier (5.32 ± 0.958 days vs. 16.22 ± 4.041 days) which was statistically significant ($p < 0.001$).

Serum IL 6 increases proportionately after surgery and it correlates well with the extent of tissue damage, approach of the operation and the complexity of the operative procedures.^[16]

Serum IL 6 level was significantly higher in patients with surgical site infections than those without postoperative wound infections which was statistically significant ($p < 0.05$).^[12] Similar outcomes have been observed in the present study too.

The sensitivity, specificity, PPV and NPV of IL 6 were found to be better than CRP on a day to day comparison postoperatively [Table 5].

The rate of infections in the present study was 36.49%, similar to 35.60% reported by Supomo.^[12] *E. coli* was isolated in most of the patients.

Conclusion

Both CRP and IL 6 correlate well with postoperative surgical site infections and can be used either alone or in combination as biological markers in postoperative patients. Chances of developing wound infections postoperatively in patients with normal CRP or IL 6 is very low and they can be discharged early. This knowledge can be of use particularly for rural surgeons with limited resources.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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