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THE SERUM IL- 6 RESPONSE TO ELECTIVE AND EMERGENCY SURGERIES

By
Ayman I . Nafeh M.D[1]. and Salma Mekhemer M.D[2].
Surgical department[1], Theodor Bilharz Institute and Chemical [2] and Clinical Pathology department ,
Cairo University, Egypt

Back ground: *Recently, a number of clinical studies have clarified the IL-6 response to trauma, burns and elective surgery. This study was carried out to evaluate the correlation of the serum IL-6 level with the injury severity in surgical cases and its value in prediction of the postoperative course and the patients outcome.*

Material and methods*: This clinical study included 60 patients, 40 of them (GI) were subjected to elective surgery [non-complicated inguinal hernia (G I a, n = 10) chronic calcular cholecystitis (GI b, n = 20) and non -complicated colorectal cancer (GI c, n=10)] and the remaining 20 patients (GII) underwent emergency surgery (intra – abdominal sepsis of non – malignant causes (GII a, n=12) and complicated colorectal cancer (GII a, n = 8).*

All patients were subjected to clinical and conventional laboratory evaluation as well as estimation of serum IL-6 two hours preoperatively and on the days ½, 1, 2, 3, 4, 5, 7, and 10 postoperatively.

Results:
Group I (elective cases): The preoperative serum IL- 6 levels in GI a & b & c were 7.95 + 1.6, 8.31 + 1.5 and 20. 8 + 5.9 pg / ml respectively. Their levels started to increase 12 hours postoperatively and reached their peaks one day after operation with significant higher levels in oncological compared to non – malignant cases. Then the levels started to decrease 2 and 3 days postoperatively to reach about the preoperative levels 3 and 4 days after operation in non – malignant and oncological patient respectively.

Group II (emergency cases): The preoperative serum IL6 levels were 225.99 + 25.30 and 260 .22 + 30.5 pg / ml in GII a & b respectively. These values started to increase postoperatively to reach their peaks one day after operation The serum levels started to decrease in the 4th and 5th days postoperatively to reach near the preoperative levels of group I.

Conclusion: *The present study proved that serum IL-6 is a sensitive non specific quantitative parameter in preoperative evaluation of surgical patients.*
- *It also reflected the magnitude of operative trauma and could predict the outcome of these patients.*

INTRODUCTION

Interleukin - 6 (IL–6) is an integral cytokine mediator of the acute phase response to diverse effects ranging from injury to malignancy [(1)]. Recently, a number of clinical studies have described the serum IL-6 elevation in response to trauma[(2)], burns[(3, 4,5)] and elective surgery[(6,7,8,9)].

The precise role of IL-6 in mediating the adverse post injury events has not yet been thoroughly understood, therefore its clinical application in diagnosis is not well established.

The aim of this study is to evaluate the correlation of the serum IL-6 level with the injury severity in surgical patients and its value in prediction of the postoperative course as well as the patients outcome.

MATERIALS AND METHODS

Groups of the study:-

This study was done in Theodor Bilharz Institute and included 60 patients,40 of them were subjected to elective surgery (group I) and the remaining 20 patients underwent their operations on an emergency base (group II).

The patients in group I (GI, n=40) including variety of cases having non-complicated inguinal hernia (GI a, n=10) chronic calcular cholecystitis (GI b, n=20) and non-complicated colorectal cancer (GI c n=10), (Table:1) .

Group II (G II, n=20) comprised 20 patients with acute abdomen of various etiology, 12 of them (G II a, n=12) were due to intra-abdominal sepsis of non- malignant causes (perforated acute appendicitis, perforated peptic ulcer, perforated divereticulitis) and the remaining 8 patients (G II b, n=8) had complicated colorectal cancer (infection, perforation and colonic obstruction) (Table: 2).

All patients in this study were subjected to routine preoperative evaluation and postoperative follow up using clinical examination, laboratory, radiological and instrumental investigations. In the meantime peripheral venous blood samples were obtained for detection of serum IL-6 levels 2hours preoperatively and on the days ½, 1, 2, 3, 4, 5, 7, 10 postoperatively. In patients who showed postoperative complications further blood samples were taken twice weekly until the patient recovered or dies.

Each blood sample was centrifuged to obtain its serum which was stored at (-40°c) until the time of IL-6 estimation.

Estimation of IL-6

- IL- 6 was measured with a commercial competitive enzyme immunoassay (ETA) kit (Accucyte Human IL –6) provided by(cytimmune science Inc.) made in USA.

RESULTS

Group I (elective cases):

The preoperative serum IL-6 levels in patients subjected to elective surgery showed variable figures (Table 1 & Fig.1) . In patients with uncomplicated inguinal hernia and chronic calcular cholecystitis, the mean of the serum IL-6 levels was 7.95 ± 1.6 pg/ ml & 8.31 ± 1.5 pg/ ml respectively. The highest preoperative serum IL-6 levels were seen in the oncological patients in which their mean was about 3 times of the other cases in this group (20.8 ±5.9 pg/ ml) but this increase was statistically insignificant.

Twelve hours postoperatively, the serum IL- 6 levels were markedly elevated in all patients of this group. The peak levels were reached one day postoperatively in patients with uncomplicated inguinal hernia, laparoscopic and open cholecystectomy.The means of their serum IL-6 level peaks were 40.62 ± 4.4 , 48.82 ± 5.1 and 53.82 ± 5.9 pg/ml respectively. In only one case of laparoscopic cholecystectomy which was converted to open surgery due to marked adhesions which needed prolonged and extensive dissection, the increase of the serum IL-6 level was remarkably more than in other cases of cholecystectomy and its peak after one day postoperatively was 101.24 pg/ ml.

In non – malignant cases of group (GI a & b) serum IL-6 levels started to decrease on the second day postoperatively to reach near its preoperative levels 3 days after operations. There was an exception of this pattern noticed in a case of laparoscopic cholecystectomy which was complicated with subhepatic intra-abdominal abscess (diagnosed clinically and documented by ultrasound examination) due to bile collection, where the level of serum IL-6 remained high for 10 days and did not decrease except after percutaneous ultrasnographic guided aspiration of the collection and systemic antibiotic administration.

- In oncological cases of group I (GI c) the peak of serum IL-6 levels were reached one day postoperatively with a mean of 291.52± 30.5 pg/ ml (10 times of its preoperative levels). These levels started to decrease on the third day postoperatively to reach near its preoperative levels 4 days after surgery. Also, one patient among these cases with complicated anastomotic leakage did not show obvious decrease in serum IL-6 level except after healing of the site of leakage one month postoperatively.

Group II (Emergency Cases):

In this group (Table 2, Fig. 2) the preoperative serum IL-6 levels of patients having non - malignant acute abdominal sepsis (G II a) were high with a mean of 225.39 ± 25.30 pg/ml, patients who had colorectal cancer complicated with infections, perforation or colonic obstruction (GII b) showed higher levels of serum IL-6 with a mean of 260.42 ± 30.5 pg/ml.

Twelve hours postoperatively, the non-malignant cases showed increase of the serum IL-6 levels with further increase of their levels to reach their peaks one day postoperatively with a mean of 400.25 ± 25 pg/ml. Their levels started to decrease on the fourth day to reach levels almost near the levels of the non emergency cases in group I seven days postoperatively. Among these patients, only one case complicated with severe wound and chest infection in which the serum IL-6 level remained high for 2 weeks, then started to decrease gradually while the patient was improving clinically till the serum level reached about the preoperative non emergency level.

In cases with complicated colonic cancer, the serum IL-6 levels started to increase 12 hours postoperatively and reached their peak at the end of the first day with a mean of 560.62 ± 50.5 pg/ ml. Their levels started to decrease on the fifth day postoperatively to reach levels almost near those of the preoperative elective malignant levels of group I ten days postoperatively. Only one case among these patients complicated with an anastomotic leakage and severe sepsis syndrome and MOF, in which the postoperative high level of serum IL-6 persisted and did not decrease until the patient died 3 weeks postoperatively.

Table 1 :- ***Pre and Postoperative serum IL – 6 levels in elective cases (group 1)***

Elective cases	*Preoperative*	*SERUM IL – 6 LEVELS (Pg / mI) Postoperative (days)*							
		½	*1*	*2*	*3*	*4*	*5*	*7*	*10*
Hernia	7.95 ± 1.6	30.82 ± 3.9	40.62±4.4	15.42± 3. 92	8.82±2.2	8.48 ± 2.8	8.42±2.78	8.12±2.82	8.02±1.92
Lap . cholecystectomy	8.31 ± 1.5	35.24 ± 4.1	48.82 ± 5.1	17.94± 4.12	11.24±2.92	10.28±2.72	10.12±2.62	9.82±2.52	8.98±2.02
Open cholecystectomy	8.31 ± 1.5	40 . 68 ± 4.8	53.82 ± 5.9	18.82 ± 4.52	13.82±3.2	12.24±3.28	11.12±3.62	10.22±3.64	8.92±2.04
Colonic cancer	20 ± 5.9	222.42± 28.4	291.52 ± 30.5	280.22±30.12	120.7±28. 82	26.92±7.22	25.88±6.22	24.28±5.92	22 ± 6.12

Table 2 , ***Pre and Postoperative serum IL – 6 levels in Emergency cases (group ll)***

Emergency cases	Preoperative	SERUM IL – 6 LEVELS (Pg / mI) Postoperative (days)							
		½	1	2	3	4	5	7	10
Non- malignant cases Intra - abdominal sepsis	225.39 ± 25.30	360. 82 ± 30. 48	400.25 ± 35.25	391.42 ± 40.22	390 . 92 ± 40.02	62.82 ± 12.28	22.82 ± 6.48	10.42 ± 3.42	8.88± 3.42
Complicated colorectal cancer	260.42 ± 30. 5	492.28 ± 42. 28	566.62 ± 50.52	449.86 ± 49. 2	530.92 ± 48.24	500.84± 46.28	70. 24 ± 14.88	25.88±6.22	23.82±6.92

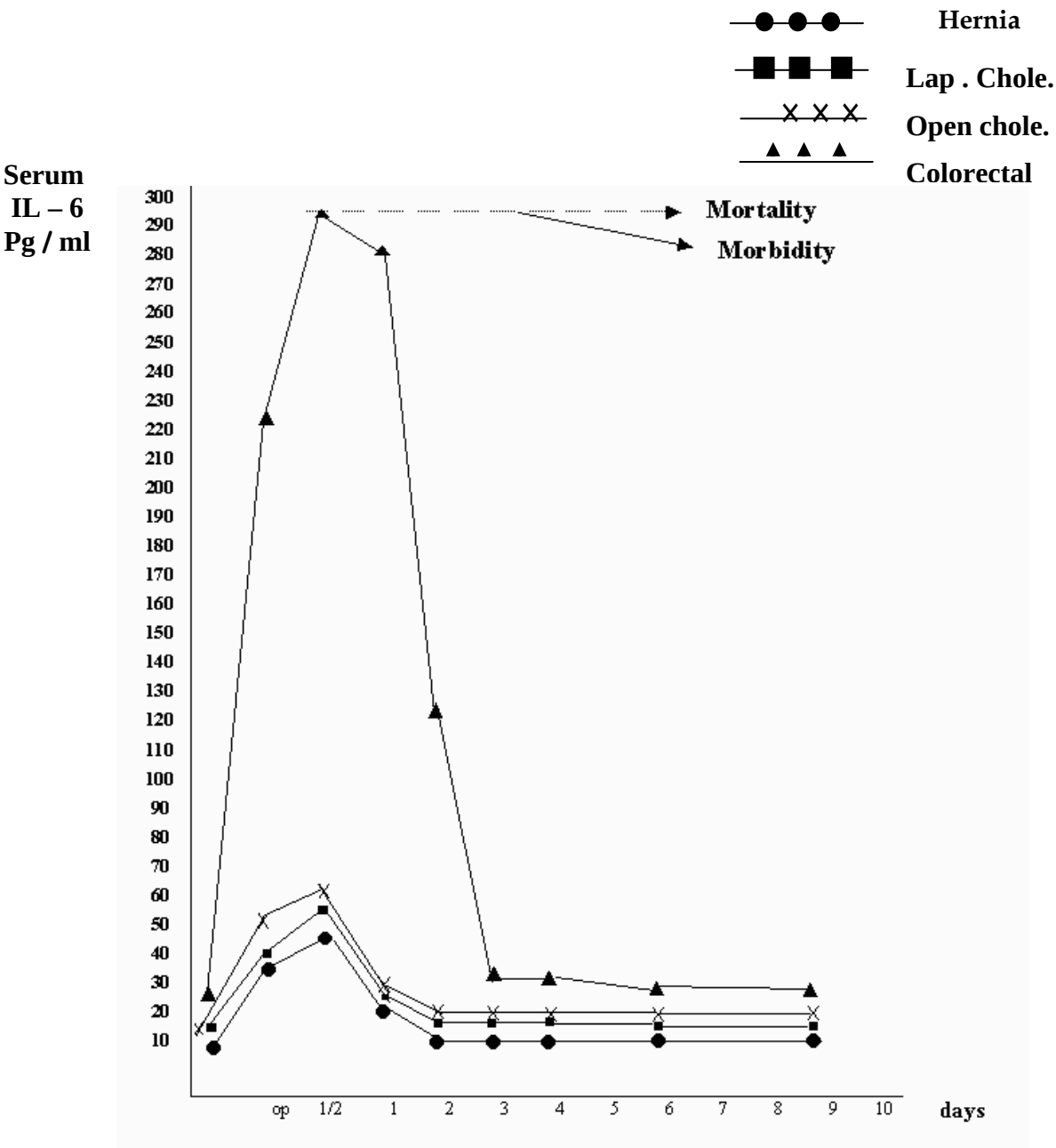

Fig . (1) : Per and Postoperative serum IL- 6 levels in elective cases (group 1)

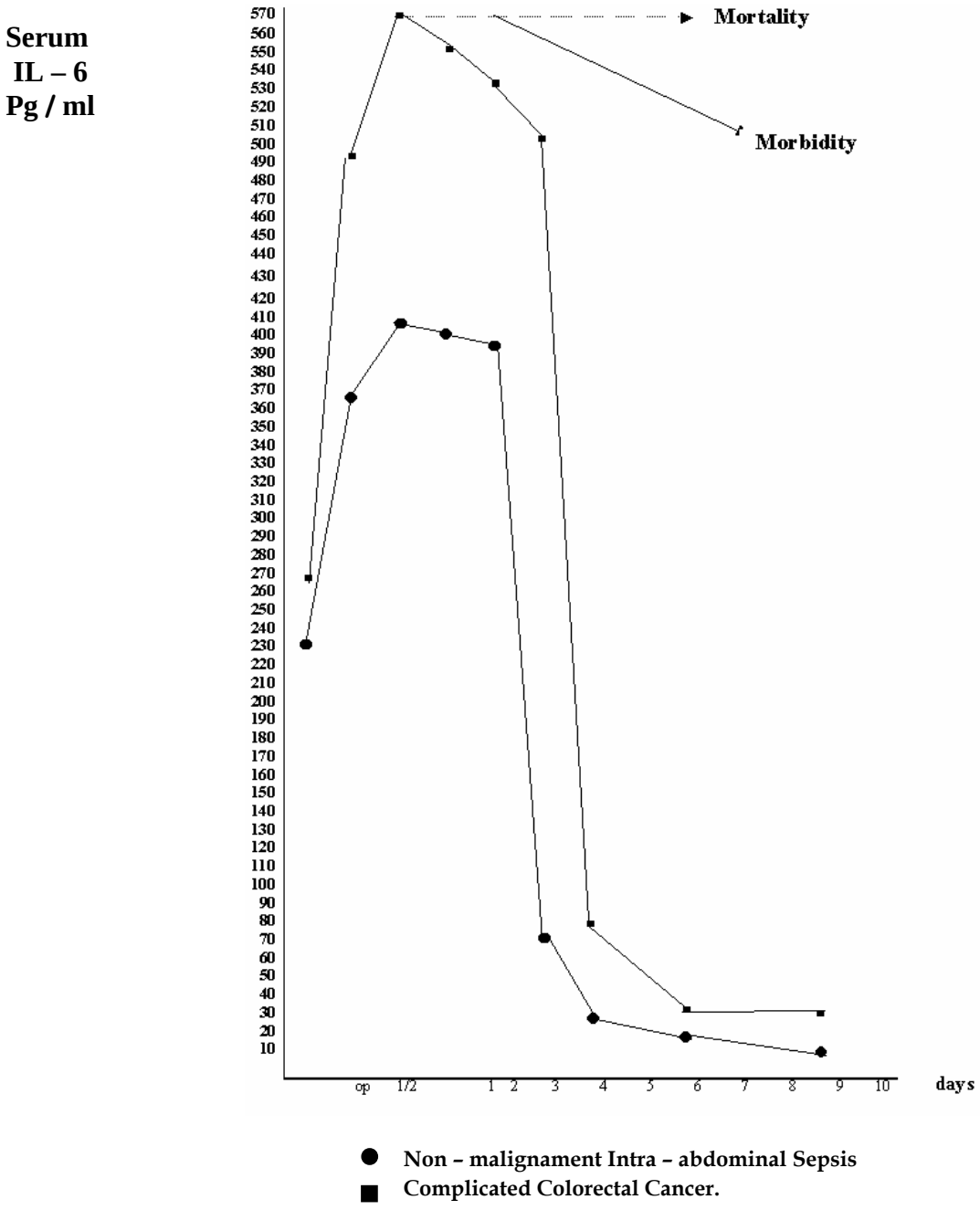

Fig (2) :Per and Postoperative serum IL- 6 levels in emergency cases (group 1l)

DISCUSSION

Interleukin – 6 is a multifunctional cytokine, expressed by variety of cells often a [10, 11] multitude of stimuli, under complex regularity control mechanisms. The exact mechanisms responsible for the production and release of IL-6 under steady – state conditions remain unclear. Interleukin- 6 appears to be expressed constitutively in humans, and low quantities can be found in the circulating blood of healthy individuals. The short half – life of IL-6 in serum (less than 1 hour) combined with the fact that IL-6 is detected constantly in blood, suggests continuous production of IL-6 [12 , 13].To date, the source of IL-6 is not entirely clear. Blood –borne IL-6 may be librated by circulating myeloid or lymphoid cells or may represent "spillover" from gut, liver, wound or other local tissues [14].

Several clinical studies proved a definite correlation between the serum IL-6 expression and each type of surgical trauma individually. In one research, the studied group of patients included varieties of elective operations and their effect on IL-6 expression. Tscope of the present study was extended to include samples of patients representing cases which the surgeon might face in surgical practice. This study included the preoperative evaluation and the postoperative follow up of elective cases as well as those underwent emergency operations using serum IL-6 and its correlation to their clinical condition.

In this study the preoperative estimation of serum IL-6 in patients with uncomplicated hernia and gall bladder stones in the elective group (GI) revealed values about those of normal individuals. In this group, the oncological patients showed higher levels about 3 folds of the elective non - malignant cases. These data revealed that the IL-6 might play a role in preoperative evaluation in elective cases.

In all these cases of GI, the serum IL-6 levels started to increase 12 hours postoperatively to reach their peaks one day after surgery. The peak levels in the malignant patients in GI was significantly higher than those of non - malignant patients ($P < 0.05$)

In patients with smooth postoperative course in this group (GI), the serum IL-6 levels returned near to each preoperative levels 3 and 4 days postoperatively in non - malignant and malignant patients respectively.

These results agreed with those reported by Slotwinski et al in 2000, who recorded higher serum IL-6 levels in malignant patients than in non - malignant ones.

- It was obvious in the present study that serum IL-6 levels in patients who had postoperative complications did not return to normal for duration corresponding to that of clinical morbidity. It was also noticed that in these complicated cases, the decrease in the serum IL-6 level occurred 2 days before their clinical improvement. These data might suggest that the serum IL-6 is more sensitive than the clinical data in the postoperative follow up.

- Suggest that the serum IL-6 is more sensitive than the clinical data in the postoperative follow up.

- Furthermore, in one of the cases subjected to laparoscopic surgery and converted to prolonged open surgery with extensive dissection due to marked adhesions the peak of serum IL-6 level one day postoperatively was significantly increased, more than the levels of other laparoscopic or open cholecystectomy in this study. These data proved that the serum IL-6 correlates well with the intensity of operative trauma.

- In emergency cases (group II), the preoperative serum IL-6 levels were significantly higher than those in elective cases ($P < 0.01$). These data went parallel with those reported by other investigators [15, 5] who reported high serum IL- 6 levels in cases with intra-abdominal sepsis.

- In the present study, emergency cases on top of malignant pathology (GIIb) still had higher levels than in non - malignant patients (G II a).

- Also, the serum IL-6 levels in emergency patients (G II) started to increase 12 hours postoperatively with further elevation to higher levels one day after operation. These high levels persisted for about 4 days and 6 days in non - malignant and malignant cases respectively. After which their levels started to decrease to reach levels near those in the elective group (G I) 10 days postoperatively.

- Once again, in this group (G II), patients who showed delayed recovery did not reveal serum IL-6 level decrease except 2 days before clinical improvement. Also, in the group of emergency patients, the serum IL-6 level did not show any decline in a single case until he died 3 weeks postoperatively.

Conclusions

This study proved that serum IL-6 is a sensitive (but non specific) quantitative parameter in the *preoperative* assessment of the surgical patients which increased proportionally with the severity of the clinical condition.

The result of the present study revealed that the serum IL-6 level is consistently correlated with the magnitude of the *operative trauma* regarding its duration and intensity.

It was also documented that the excessive and prolonged *postoperative* elevation of the serum IL-6 levels are associated with morbidity and mortality.

Recommendations

- This study might suggest the use of the serum IL-6 as a sensitive nonspecific quantitative marker in the preoperative evaluation of surgical patients besides being a sensitive accurate sensitive predictor to their outcome.

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