Change in serum interleukin-6 levels in patients after pancreatoduodenectomy for periampullary cancer

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Article Info

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Abstract

This study was undertaken to elucidate the changes in interleukin-6 concentrations in the systemic circulation of 20 patients following pancreatoduodenectomy and whether it had any predictive value for postoperative complications. Blood was drawn on the day before surgery, at fixed intervals immediately after closure of the abdomen, and on day 1, 3, 5 after surgery for the measurement of interleukin-6. Change in the serum interleukin-6 levels was observed before and after pancreatoduodenectomy and between patients with and without complications. There was no mortality, but morbidity occurred in 5 patients. Serum interleukin-6 levels peaked immediately after surgery and gradually declined to preoperative level on postoperative day 5, but it remained persistently higher in a patient who developed postoperative complication. The peak level of interleukin-6 was significantly correlated with body mass index, duration of jaundice, biliary decompression prior to surgery, operation time and hospital stay, but not with operative blood loss. In conclusion, interleukin-6 is an important stress marker for predicting the complications after pancreatoduodenectomy operation. Patient with good body mass index status, short duration of jaundice and without preoperative biliary decompression provides less operative stress, less chance of complications and shorter hospital stay.

Introduction

Pancreatoduodenectomy (PD) is a stressful surgery that carries significant morbidity and mortality. Assessment of stress and its relation to developing postsurgical complications remain to be identified.[1] Cytokines are multifunctional proteins that play an important role in initiating and maintaining the immune response. Interleukin-6 (IL-6) is a cytokine with both pro- and anti-inflammatory properties, and its release into the peripheral blood seems to be an early marker of severity of injury following major trauma or surgery.[2] In the acute phase of the inflammatory response, its pro-inflammatory properties appear to be most pronounced and play a role in initiating and re-enforcing the systemic inflammatory response. Later, its anti-inflammatory properties dominate when IL-6 acts as a down-regulator of the pro-inflammatory responses of tumor necrosis factor-a (TNF-a) and IL-1.[3] While a number of cytokines (TNF-a, IL-1) are harmful at high concentrations, it remains to be clarified to which extent the IL-6 response is beneficial to the patient.[4, 5] There are many clinical studies that describe the IL-6 response to trauma and elective surgery.[6-8] This cytokine release is related to the extent of the surgically induced trauma.[9-11] Although IL-6 is considered to be a mediator of the physiologic short-term phase reaction to injury, excessive and prolonged post injury elevations are associated with increased morbidity. Few researchers reported excessively increased plasma levels for many days and demonstrated some correlation with multiple organ dysfunctions following accidental trauma.[12-14] This study was undertaken to elucidate the changes in IL-6 concentrations in the systemic circulation following pancreatoduodenectomy, and whether this mediator possessed any predictive value for postoperative complications.

Patients and Methods

Patients

Twenty patients (12 males, 8 females; average age 48 years) who have undergone pancreatoduodenectomy for the carcinoma of head (n=2), lower bile duct carcinoma (n=4), carcinoma of ampulla of the Vater (n=11), solid pseudopapillary tumor of pancreas head (n=1) and duodenal GIST (n=2) at the Division of Hepatobiliary and Pancreatic Surgery, Department of

Surgery, Bangabandhu Sheikh Medical University from July, 2015 to December, 2016. The patient had been scheduled for pancreatoduodenectomy on the basis of clinical findings and images but the procedure converted to triple bypass because of per-operative assessment of irresectability were excluded from the study.

Collection of data

Data on demography, clinical and biochemical parameters, investigations, and management were recorded in the data collection sheet. Blood for cytokine measurement was drawn on the day before surgery and at fixed intervals immediately after closure of abdomen, and on day 1, 3, 5 after surgery. After collection of blood, the serum was collected by centrifuging the samples and finally stored at –80°C until analysis.

Quantification of IL-6 in serum

Serum concentrations of IL-6 were measured using the commercially available enzyme amplified solid-phase ELISA assays. The assay was performed as described by the manufacturer. All samples were analyzed in double and no freeze-thaw cycles were performed during sample handling.

Change in serum IL-6 levels before and after PD had been observed. The differences in IL-6 levels between patients without complications and patients with complications had been calculated. Correlation had been sought between factors those were seemed to be related to patients postoperative outcome (BMI, duration of jaundice before surgery, doing of preoperative biliary decompression, operation time, preoperative blood loss) and peak levels of IL-6. Correlation between the hospital stay and peak levels of IL-6 had also been sought.

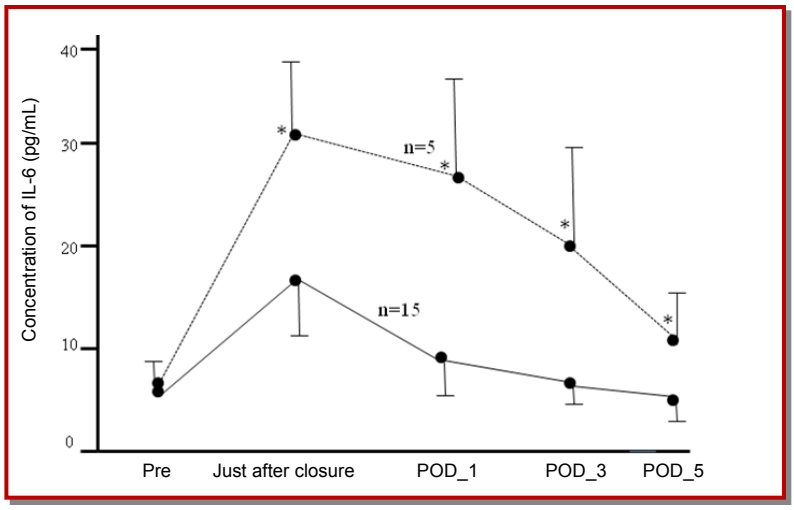

Figure 1: Changes in serum IL-6 levels in patients with complications (---) and without complications (—) after pancreatoduodenectomy. *p value is <0.05

Statistical analysis

Data are presented as mean and standard deviation with range. The results were compared using student or ANOVAs t-test as appropriate. Correlation analysis was used to assess the relationship between levels of IL-6 and pre-, per-, and post-operative factors those are related to stress production. It was done using the multiple regression analysis system. All statistical analyses were performed using SPSS statistics. P value of less than 0.05 was considered as statistically significant.

Results

The average body mass index of patient was 20.8 with a range of 14.2 to 28.1. Six patients had diabetes and 2 patients had hypertension. The mean duration of jaundice before surgery is 3.1 months with a range of 0.5 to 6.5 months. Nine patients were undergone biliary decompression by ERCP and stenting before surgery.

The preoperative mean hemoglobin level was 11.4 ± 0.8 g/dL. The preoperative liver functions of 20 patients were: total serum bilirubin; 4.6 ± 4.1 mg/dL, total serum albumin 3.4 ± 0.6 g/dL, prothrombin time 13.5 ± 1.2 sec, and international normalized ratio (INR) 1.1 ± 0.1. The time required for operation was 4.9 ± 0.6 hours. The mean operative blood loss was 323 ± 112 mL. There was no operative mortality, but the morbidity occurred in 5 patients; major wound infection required secondary suturing in 1, bile leakage with peritonitis in 1, bile leakage with localized collection in 1 patient and pancreatic leakage with wound dehiscence in 2 patients. All patients were recovered from complication by conservative treatment.

Changes in serum IL-6 concentrations

Serum IL-6 levels peaks (25.7 ± 13.7 pg/mL) immediately after surgery and then gradually declined to preoperative level (6.7 ± 2.7 pg/mL) within 5th postoperative day. Serum IL-6 levels rose persistently after PD in a patient with postoperative complication than without complication (Figure 1). The difference is statistically significant between these two groups. The peak level of IL-6 is significantly correlated with body mass index, preoperative duration of jaundice, operation time and postoperative hospital stay (Figure 2) but not with operative blood loss (data not shown). The peak level of IL-6 is significantly higher ($p<0.5$) in a patient who underwent biliary decompression (33.1 ± 13.7 pg/mL) than who did not (17.0 ± 5.3 pg/mL). Five out of 9 patients with preoperative biliary stenting had high level of serum IL-6 levels who suffered from complications after surgery.

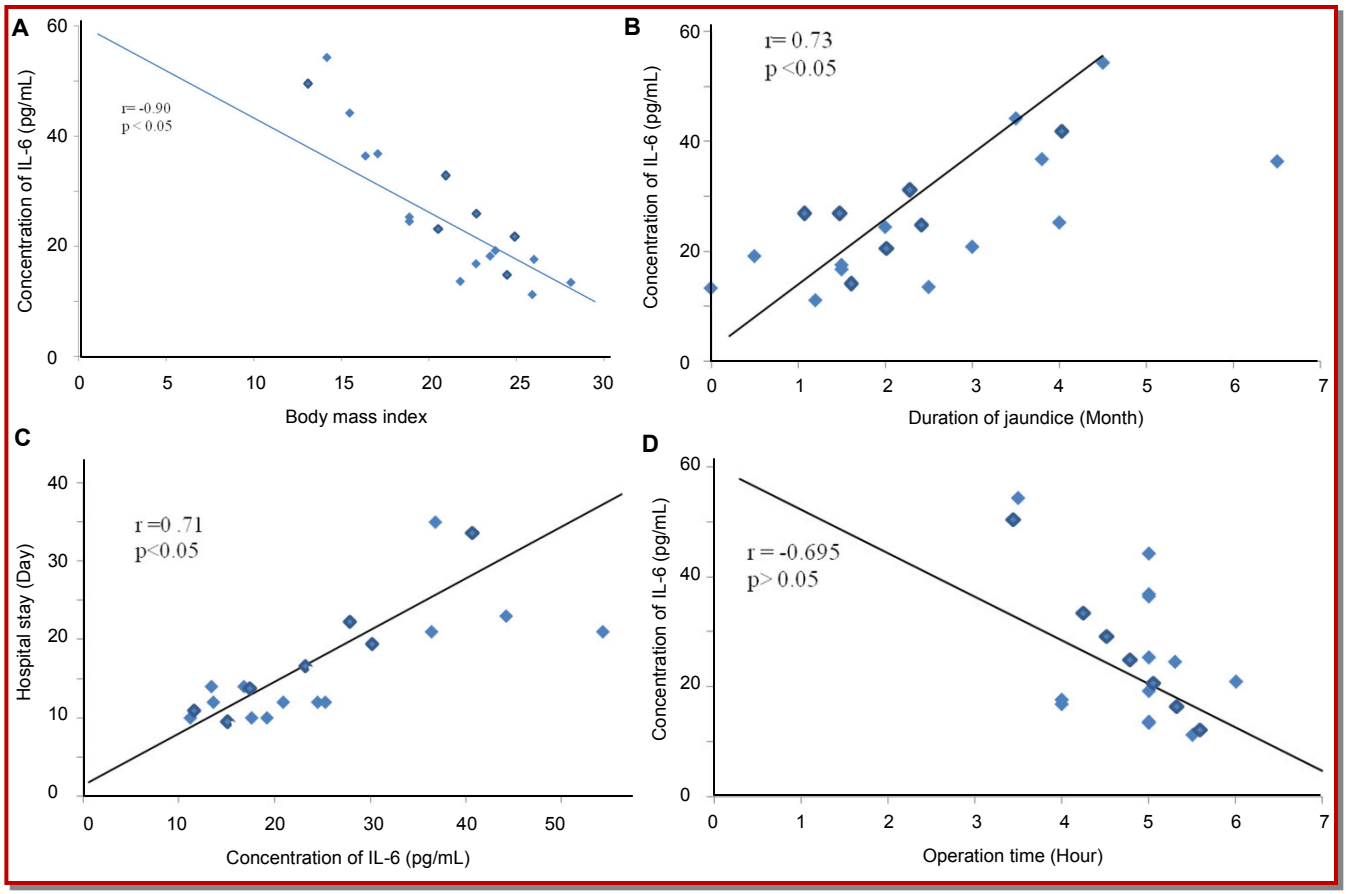

Figure 2: Correlation between body mass index (A), duration of jaundice (B), hospital stay (C), and operation time (D)

Discussion

Our observation is that the serum IL-6 reached to its peak level immediately after closure of abdomen. This peak level of serum IL-6 is significantly influenced by patient's BMI value, duration of jaundice prior to surgery, biliary stenting before surgery and operation time. It is also noted that the patient who had very high levels of IL-6 in the early postoperative developed postoperative complications like infections and anastomosis leakage. It means that the patient who had poor preoperative nutrition status, who spent a longer time with jaundice, the patient who underwent biliary decompression before surgery and who need longer time for surgery encountered to high surgical stress and developed postoperative complications.

Su et al. analyzed 101 patients who underwent PD according to presence or absence of infectious postoperative complications.[15] Nineteen peri-operative variables were analyzed to identify risk factors associated with postoperative infectious complications. Postoperative infectious complications occurred in 56 patients (55%); among them 29 had serious infectious morbidity, including bacteremia (13%), intra-abdominal infection (18%) and pneumonia (12%). One patient (1%) died of multiple organ failures subsequent to a severe septic attack. Only body mass index differed significantly between patients with and without serious infection. The results of several studies reveal that preoperative biliary drainage is associated with increased morbidity and mortality rates especially the infective complications in patients undergoing pancreaticoduodenectomy.[16-18] They suggest that preoperative biliary drainage should be avoided whenever possible in patients with potentially resec -table pancreatic and peripancreatic lesions. Reports also evident that a long time to perform and duration of surgery is frequently cited as a major risk factor for postoperative complications.[19-20]

Our results support all these findings published in recently. These factors are strongly correlated with peak levels of serum IL-6 levels which is designated as stress marker in several reports.[2-3, 6-11] Although several studies demonstrated that substantial amount of operative blood loss and intraoperative blood transfusion is associated with postoperative morbidity and mortality after surgery.[21, 22] Our study could not show the relation of blood loss with operative and postoperative complications as our operative loss was minimum. Another observation

of the present study, the high peak serum IL-6 level is also related to prolong hospital stay of the patient. The long hospital stay of those patients required for the management of postoperative complications.

Conclusion

Early measurement of serum IL-6 will provide an idea of the magnitude of stress occurred during operation and also serve as a good predictor of post -operative complications after PD. Patient with good body mass index status, short duration of jaundice and without preoperative biliary decompression, short operation time provides less operative stress, less chance of complications and shorten the hospital stay.

Ethical Issue

Written informed consent was obtained from the patients or the next of kin. The local ethics committee approved the study.

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