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Response Of Serum Interleukin - 6 Following Minimally Invasive And Open Surgery For Renal Cell Carcinoma

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I. Introduction

Major surgical procedures like nephrectomy (partial/radical) initiate physiological stress on the body's immune system which depends on the extent of invasiveness of surgery. Though laparoscopy benefits by small skin incision, still tissue manipulation and division are somewhat crude as compared to robotic surgery which carefully divides and repairs tissue hence, it is expected that surgical stress should be least in robotic.

IL-6 is strong and an earlier marker in the cascade of acute phase reaction following surgery and is known to be an important mediator of body's response to operative trauma.[1,2] It has positive correlation to extent of trauma during surgery. Additionally, IL-6 by stimulating the production of vascular endothelial growth factor and angiogenic pathways plays an important role in tumor growth, recurrence, and metastasis. Therefore, it is thought that in patients undergoing laparoscopic surgery for neoplasms there can be more oncological control conferred by preservation of these angiogenic mechanisms. Our study was carried out in a prospective manner to compare the immune response to surgical stress among patients of RCC being managed surgically either by open technique or minimally invasive technique by the determination of important immunological marker IL-6.

II. Methods

The study was conducted in Post Graduate Institute of Medical Education and Research from January 2017 to June 2018 after assessing their eligibility according to the inclusion criteria.

Operations and techniques

All patients were operated after administration of general anaesthesia using similar protocol. The da vinci SI surgical system was used for all robotic procedures. Standard LN was done transperitoneally, after creating closed pneumoperitoneum to 12 – 15 mmHg. Two 10-12 mm ports and one/two 5mm ports were placed using standard port placement techniques in both laparoscopic and robotic surgeries. The specimen was extracted in an endobag made from standard urobags available in the market, with the most inferior trocar site as the preferred surgical site. The open nephrectomy procedures were performed by transperitoneal approach through subcostal area, with surgical incision varying from 12-15 cm depending on the patient's body habitus.

All patients received perioperative antibiotic prophylaxis. In postoperative period uniform adequate analgesia was provided to all the patients. 26 eligible patients of RCC underwent laparoscopic/robotic or open nephrectomy with allocation based on standard oncologic guidelines. The patients were divided into two groups group 1 and group 2, with patients in group 1 underwent open surgery for RCC and patients in group 2 underwent minimally invasive surgery (Figure 1).

Inclusion Criteria

(1) Patients suspected to have renal cell carcinoma on basis of history, physical examination, and imaging [Colour doppler, CT scan with contrast enhancement more than 15 Hounsfield units (HU) or MRI demonstrating renal masses].
(2) Patient undergoing nephrectomy (partial/radical/NSS) were enrolled for the study.

Exclusion Criteria

(1) Age < 18 yrs.
(2) American Society of Anaesthesiologists classification (ASA)> 3.
(3) Use of immunosuppressive drugs.
(4) History of autoimmune disease.

(5) History of immunological diseases requiring systemic administration of corticosteroids.
(6) Patients with synchronous cancers at another site.
(7) Severe disease of respiratory or cardiovascular system.

All the participants were explained about the surgery along with the complications in detail and written consent was obtained. The relevant clinical history of the patients along with the operative details and postoperative events were recorded prospectively.

Study Protocol

After recruitment of the patients, three EDTA blood samples were collected for each group. Baseline measurements of plasma cytokine level i.e., interleukin-6 (time point T0) were taken preoperatively. In the postoperative period, the blood samples were collected at 24 and 72 hrs (time points T1 and T2). The blood samples were carried to the laboratory in the cold chain. In the laboratory the samples were centrifuged and the plasma was stored at – 20 degrees Celsius till further analysis.

Measurements

The plasma concentrations of cytokines were determined by solid phase Enzyme linked immunosorbent assay by employing a commercially available kit. The procedure was followed as per the directions given by the manufacturer. The technique was based on the use of monoclonal antibodies directed against different epitopes of the cytokine.

Statistical Analyses

Descriptive analysis was used to summarize data using frequency, percentages, mean ± standard deviation (S.D.) with 95% confidence interval and median. For normally distributed data, analysis of variance (ANOVA) was applied for statistical analysis of three groups. For skewed data, non parameteric tests i.e., Mann-Whitney *U*-test and Kruskal-Walli's test were applied. For categorical data comparisons were made by Fisher's exact test. Serum concentrations of IL-6 were compared preoperatively and at postoperative day 1 and day 3 within the group and between groups using ANOVA or Kruskal- Walli's test. All the statistical tests were two-sided. 'p' value less than 0.05 was considered statistically significant.

III. Results

Out of the 26 patients included for final analysis, group 1 consisted of 13 patients undergoing open nephrectomy either partial (1) or radical (12) while in group 2 eight patients underwent standard transperitoneal laparoscopic radical nephrectomy (LN), and 5 underwent robot assisted nephron sparing surgery (NSS). The patients recruited to either group had a comparable demographic profile. There were no intraoperative and postoperative complications reported in either group which indicates that robotic/laparoscopic nephrectomy is as safe as open nephrectomy.

A statistically significant difference was seen in serum concentration of IL-6 when a comparison was made among the different groups at various time points postoperatively. There were significant alterations in serum concentrations of IL-6 in both open and minimally invasive group. After maximal elevation observed at 24 hours, the levels of IL-6 declined significantly at 72 hours, however postoperative levels were still more than the baseline levels. These changes in dynamics of serum IL-6 levels with time were found to be statistically significant in all the groups i.e., the open ($p=0.003$), laparoscopic ($p=0.007$) and robotic ($p = 0.002$) (Table 1). Additionally, on intergroup comparison the groups did not show any significant difference at various time points (Table 2) and the only difference between groups occurred at 72 hours when the serum IL-6 concentration was significantly lower in the robotic group than in the laparoscopy group ($p=0.048$) (Figure 2).

IV. Discussion

Surgical trauma is known to stimulate the activation of cytokines which act locally as well as at systemic levels. In this prospective study we have tried to find out/compare the extent of stress response between open nephrectomy and minimally invasive nephrectomy (these include laparoscopic and robotic). Out of 26 patients included in the study 13 had undergone open surgery (group 1) and rest 13 had undergone minimally invasive surgery (group 2).

The changes in dynamics of serum IL-6 levels were found to be statistically significant in all the groups i.e., open ($p=0.003$), laparoscopic ($p=0.007$) and robotic group ($p=0.002$) which implies that measurement of IL-6 levels is useful as objective marker of surgical stress. This finding is consistent with the findings of Miyake et al[3] which states that measurement of IL-6, IL-10 and granulocytic elastase is useful as markers of surgical trauma.

Furthermore, levels of IL-6 had not been analysed previously in association with robot assisted NSS/ nephrectomy. The present study has demonstrated lower rise of IL-6 levels among patients undergoing robot

assisted NSS/nephrectomy which implies attenuated inflammatory response following robotic procedure. We found no significant difference in serum IL-6 after open and laparoscopic nephrectomy, although serum IL-6 did rise after surgery in both the groups, a finding confirmed by Mehigan[4] and colleagues who also found no significant difference between the approaches for colon cancer by comparing the levels of IL-6 perioperatively. This is further supported by work of Dunker et al[5] and Hewitt et al[6] who found lower IL-6 levels after colon resection laparoscopically in patients of bowel disease and colon cancer respectively.

Cruickshank et al[7] observed direct correlation between extent of trauma during surgery and level of IL-6 secretion in circulation. They noted increase in levels of IL-6 after incision with peak at 6 to 12 hours after surgery in various abdominal surgical procedures. Likewise, in present study, levels started increasing after surgery with maximum concentration of IL-6 found at 24 hours postoperatively. The rise at 24 hours followed by a downward trend, with differences being significant statistically, at 72 h after surgery in both laparoscopy and robotic group (p=0.048).

Robot assisted NSS/nephrectomy leads to a less pronounced increase in the level of serum IL-6 when measured at 72 hours as compared with laparoscopic nephrectomy, which may suggest the lesser interference of Robot assisted NSS/nephrectomy with the immune system as compared to the laparoscopic nephrectomy. This relatively weaker immune system activation may translate as a more rapid functional recovery.

V. Conclusion

IL-6 showed lesser fluctuation of immune response in robotic group as compared to laparoscopy group. This observation suggests the immunological benefit of robotic surgery compared to open surgery which is an additional advantage, over and above the existing benefits of minimally invasive surgery. However, more studies including more stress related markers in blood and including a greater number of patients shall help in understanding the role of immune response in Robot assisted NSS/nephrectomy.

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Table 1: Measured analyte concentrations (pg/ml) of IL-6 at different time points for open, laparoscopic, and robotic surgery

Variable	Time	Mean	Std. Deviation	p value*
IL-6 (open)	T0	27.0231	68.76856	**0.003**
	T1	66.2077	61.07211	
	T2	51.63	72.893	
IL-6 (laparoscopic)	T0	23.7250	49.87991	**0.007**
	T1	51.0375	36.56016	
	T2	12.38	6.265	
IL-6 (robotic)	T0	3.2800	2.92780	**0.002**
	T1	91.5800	53.53921	
	T2	22.70	8.935	

*Kruskal- Wallis Test

Table 2: Difference between levels of IL-6 according to type of surgery pre and post –op at 24 and 72 hours

Open vs Laparoscopy	**Open**		**Laparoscopy**		**p value***
	Mean	**SD**	**Mean**	**SD**	
T0	27.02	68.76	23.72	49.87	0.690
T1	66.20	61.07	51.03	36.56	0.772
T2	51.63	72.89	12.38	6.26	0.346
Open vs Robotic	**Open**		**Robotic**		
	Mean	**SD**	**Mean**	**SD**	
T0	27.02	68.76	3.28	2.92	0.301
T1	66.20	61.07	91.58	53.53	0.257
T2	51.63	72.89	22.70	8.93	0.521
Laparoscopy vs Robotic	**Laparoscopy**		**Robotic**		
	Mean	**SD**	**Mean**	**SD**	
T0	23.72	49.87	3.28	2.92	0.826
T1	51.03	36.56	91.58	53.53	0.143
T2	12.38	6.26	22.70	8.93	**0.048****

*Mann Whitney U Test **Significant