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"COMPARATIVE STUDY OF PRE-OPERATIVE AND POST-OPERATIVE LEVELS OF INTERLEUKIN-6 IN PATIENTS ADMINISTERED GENERAL V/S REGIONAL ANAESTHESIA"

Anaesthesiology

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ABSTRACT

Introduction: The surgical stress response significantly impacts IL-6 levels and overall recovery. Different anaesthetic techniques used in surgery have differing impacts on the post-operative systemic inflammatory response and rate of post- operative infective complications. (1-3). **Aim/Purpose:** To examine the relationship between different anaesthetic techniques, i.e. General v/s Regional Anaesthesia and the associated postoperative systemic inflammatory response in patients undergoing a surgical procedure using Interleukin-6 as a biomarker of inflammation. **Material And Methods:** This was a PROSPECTIVE STUDY conducted in patients posted for elective surgeries under General Anesthesia(GA)and Regional Anaesthesia (RA) at Shadan institute of medical sciences, General hospital Hyderabad. Two groups comprised of 30 patients of both genders falling in the age group of 18-60 years, 2 venous blood samples are to be collected for each patient with the 1st sample being collected preoperatively 2 hours prior to surgery and 2nd sample being collected 12 hours postoperatively. The serum levels of Interleukin-6 are measured. **Results:** A total of 60 patients grouped in to Group R and Group G, 30 each, statistical analysis of Preoperative and Postoperative IL-6 Levels done. P Value (t-test) Pre op IL-6 is 0.017 and post op IL-6 is <0.001. A positive correlation was observed between Group G and Group R ($r=0.45$; $p<0.001$). **Conclusion:** The significant rise in IL-6 levels postoperatively in the GA group suggests a more pronounced inflammatory response to surgical stress. which can correlate to increased postoperative pain, delayed recovery, and higher risk of complications.

KEYWORDS

IL-6, GA, RA.

INTRODUCTION:

Surgical stress response is a complex physiological reaction involves neuroendocrine, metabolic, and inflammatory changes designed to preserve homeostasis and promote recovery. The magnitude of the stress response varies with the extent, site and type of surgery, duration of surgery, **Type of Anaesthesia** administered, and individual patient factors. Understanding the stress response is crucial, as it impacts postoperative outcomes, including immune function, wound healing, and recovery. The magnitude of post-operative systemic inflammatory response resulting from surgical stress has been observed to be significantly associated with varying severity of short-term and long-term outcomes impacting the patients' morbidity and mortality. Cytokines, including tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), and interleukin-10 (IL-10), are markers of systemic inflammatory immune response. They are key modulators of inflammation in the body and help to determine the extent of tissue damage secondary to the immune system activity.(4)

IL-6 And Its Role:

IL-6 is produced by various cells, including macrophages, endothelial cells, and fibroblasts, in response to injury and infection. (5,6)

Effects: IL-6 stimulates the acute-phase response, increases the production of CRP . Changes in circulating IL-6 levels may not be significant within 30 – 60 minutes of the procedure.

However, the concentration increases significantly around 2 – 4 hours postoperatively and reaches a peak around 24 hours after administration of general anesthesia and it remains so for 48-72 hours postoperatively. (7-10) Elevated IL-6 levels are associated with increased perioperative morbidity and mortality. Therefore, in the perioperative setting, IL-6 emerges as a promising biomarker for assessing the magnitude of surgical stress and the subsequent inflammatory response. It is to be noted that interleukin-6 (IL-6) is a nonspecific marker which specifies inflammatory response of the body and is not diagnostic of any disease or disease process. (11-13)

Effects Of Anaesthesia On Stress Response:

General Anaesthesia (GA):

Mechanism: GA involves the use of inhalational or intravenous agents to induce unconsciousness, analgesia, and muscle relaxation.

Effects on Stress Response:

Sympathetic Blockade: GA agents like propofol and volatile anaesthetics attenuate the sympathetic response, reducing catecholamine release.

Cortisol Response: GA partially suppresses the HPA axis, leading to a moderated cortisol response.

Cytokine Modulation: Some GA agents may influence cytokine production, but the effects are variable and agent-dependent.

Regional Anaesthesia (RA):

Mechanism: RA involves the use of local anaesthetics to block nerve conduction, providing analgesia and muscle relaxation in specific body regions .

Effects On Stress Response:

Sympathetic Blockade: RA provides effective sympathetic blockade, reducing catecholamine release and maintaining hemodynamic stability.

Cortisol Response: RA significantly attenuates the cortisol response compared to GA, leading to lower perioperative cortisol levels.

Cytokine Modulation: RA has been shown to reduce the release of pro- inflammatory cytokines, including IL-6, potentially improving postoperative outcomes.

The surgical stress response significantly impacts IL-6 levels and overall recovery. Different anaesthetic techniques used in surgery have differing impacts on the post-operative systemic inflammatory response and rate of post- operative infective complications. (1-3).

Rationale And Purpose Of This Study:

The goal of this study is to elicit the effects of various anesthetic techniques (GA v/s RA) on inflammatory cytokine (IL-6) production

among patients undergoing surgery as elevated IL-6 levels have been associated with an increased risk of postoperative complications, such as SSI's, systemic inflammatory response syndrome, and organ dysfunction.Understanding these mechanisms helps optimize anaesthetic management to enhance patient recovery and reduce complications.

Interleukin-6 (IL-6)
Interleukin-6 (IL-6) is a cytokine involved in the regulation of immune responses, inflammation, and hematopoiesis.

Normal Serum Level: In healthy individuals, the normal serum IL-6 level is typically low, ranging from <1 pg/mL to 5 pg/mL. However, these values can vary slightly depending on the laboratory and assay methods used.

Significance:
Immune Response: IL-6 plays a crucial role in the acute phase response, stimulating the production of acute phase proteins (e.g.CRP) by the liver.

Inflammation: It is a key mediator of inflammation, being rapidly produced in response to infections, injuries, and other inflammatory stimuli.

Hematopoiesis: IL-6 influences the differentiation and proliferation of hematopoietic cells.

Disease Marker: Elevated IL-6 levels are associated with various pathological conditions, including infections, autoimmune diseases, chronic inflammatory diseases, and cancers.

Surgical Stress: IL-6 is a useful biomarker for assessing the inflammatory response and tissue injury following surgical procedure.

Methods of Measurement:
IL-6 levels in blood samples can be measured using several methods, each with varying degrees of sensitivity, specificity, and practicality:

Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescent Immunoassay (CLIA), Electrochemiluminescence (ECL), Multiplex Cytokine Assays, Flow Cytometry:

MATERIAL AND METHODS:
This was a PROSPECTIVE STUDY conducted in patients posted for elective surgeries under General Anaesthesia (GA)and Regional Anaesthesia(RA) at Shadan institute of medical sciences, General hospital, Hyderabad with Study duration of 24 months from June 2022 – May 2024.

Inclusion Criteria:
1. ASA Grade I & II
2. Elective surgeries under GA or RA.

Exclusion Criteria:
1. Uncontrolled comorbidities
2. Emergency surgical procedures
3. Patients with septic foci
4. Immunocompromised status
5. ASA Grade III & IV
6. Patients on steroid therapy

Study Methodology:
After fulfilment of institutional protocols and approval of the Ethical Committee, with written informed consent from patient, a RANDOMISED PROSPECTIVE PATIENT STUDY is being conducted with a SAMPLE SIZE of 60 over a period of 24 months, grouped into Group G and Group R.

Each group is comprised of 30 patients of both genders falling in the age group of 18-60 years. Two venous blood samples are to be collected for each patient with the 1st sample being collected preoperatively 2 hours prior to surgery and 2nd sample being collected 12 hours postoperatively. The serum levels of Interleukin-6 are measured. Values < or =1.8 pg/mL are considered normal.

Study Protocol:
Only the surgeries with a duration of >1 hour will be included.

No special preparations are needed for the IL-6 test as it is a routine blood test with minimal risks.

All patients were fasted for 8hrs and received premedication of Pantoprazole 40mg IV before entering the operating room.

On shifting to the operation theatre, a 3-lead ECG monitoring, pulse oximeter and an automated NIBP monitor was used. An 18 gauge intravenous cannula was placed before proceeding with the general or spinal anesthesia.

In Group R: Spinal anesthesia was performed with the patient in the sitting position under aseptic conditions. The skin in the L2-L3 area was infiltrated by 1% lidocaine (20 mg) and spinal needle was inserted through the L2–L3 interspace. After return of clear cerebrospinal fluid, 10-15mg of 0.5% heavy bupivacaine and 15mcg of Fentanyl were administered intrathecally slowly via 25G Quincke spinal needle.

In Group G: Premedication was given with Inj. Glycopyrrolate 0.5mg IV, Inj. Ondansetron 4mg IV and fentanyl (2 mcg/kg). GA was induced by propofol (2 mg/kg) and muscle relaxation was done with nondepolarizing muscle relaxant (Inj. Vecuronium 0.1mg/kg). Anesthesia was maintained with sevoflurane (1.0–2.0 vol% end-tidal concentration) and oxygen/N2O mixture of 50%-50%. Controlled mechanical ventilation (with Drager model) was adjusted to achieve normocapnia and an SpO2 of more than 96%.

Monitoring included HR, Systolic and diastolic BP and SpO2.

5cc of Peripheral venous blood samples were collected from upper extremities veins 2hours before surgery and 12hours postoperatively. From the blood samples we determined the preoperative and postoperative value of pro-inflammatory cytokine Interleukin-6 (IL-6).

Blood samples were taken in dry test tubes and then immediately centrifuged at 3000 rpm for 10 minutes to separate serum from blood. to the freezer under -25 Co. After one day of freezing, incubator was used to prepare the serum for analyzing the serum level of IL-6 by using an automated machine which uses C.L.I.A reader using spectrophotometry. Specificity and sensitivity of the kit were 90% and 95% respectively.

Study Statistical Analysis Plan:
Data management and statistical analysis were done by using Statistical Package for the Social Sciences (SPSS) version 22.
- Categorical data was compared by using Chi-square test ($\chi 2$). (ANOVA) test and independent sample t test used to perform relations between the mean and variables.
- Significance was assessed at 5% level of significance.
- The p-value <0.05 was considered significant.

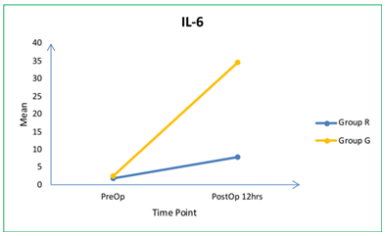
RESULTS:
A total of 60 patients included in the study,
Most of the patients fall in the age group of 19-30yrs (36.6%).
Out of 60 patients included in the study 29(48.3%) patients were males and 31 (51.66%) were females.

Table 1: IL-6 Levels In Preop And Postoperative Period In Both Groups.

IL-6	Group		P Value (t-test)
	Group R	Group G	
Pre Op	1.88 ± 0.997	2.48 ± 0.908	0.017
Post Op 12hrs	7.82 ± 5.149	34.73 ± 11.505	<0.001

Group R represents patients undergoing Regional Anaesthesia.
Group G represents patients undergoing General Anaesthesia.

- **Preoperative and Postoperative IL-6 Levels:** IL-6 levels are seen to rise significantly in Group G as compared to Group R.



Graph 1: IL-6 levels in preop and postoperative period in both groups.

DISCUSSION:

This study was conducted to understand effects of anesthesia on immune response and compare the effects of various anesthetic techniques on serum level of cytokine IL-6.

IL-6 Levels:

Preoperatively, IL-6 levels were slightly higher in the GA group (2.48 ± 0.908 pg/mL) compared to the RA group (1.88 ± 0.997 pg/mL). Postoperatively, there was a marked increase in IL-6 levels in both groups, but the increase was significantly greater in the GA group (34.73 ± 11.505 pg/mL) compared to the RA group (7.82 ± 5.149 pg/mL).

The significant rise in IL-6 levels postoperatively in the GA group suggests a more pronounced inflammatory response to surgical stress. This can be attributed to the fact that GA, unlike RA, does not effectively block the neuroendocrine stress response, leading to higher levels of stress-induced cytokine release. The RA group, benefiting from a more targeted sympathetic blockade, showed a more controlled and attenuated inflammatory response.

These finding are consistent with those of previous studies which demonstrated that surgical trauma and general anaesthesia play important roles in postoperative release of inflammatory cytokines than other types of anesthesia. [14,15]

According to a previous finding by **Zhang J et al**. during general anesthesia, intraoperative pain as well as surgical stress, leads to increased adrenergic nerve activity and plasma concentration of catecholamine followed by cytokine release due to an autonomic response. [16]

Previous studies have also confirmed that serum level of cytokines are regulated and further activated by inflammatory response during anesthesia induction directly affecting the immune system or activating the hypothalamic-pituitary- adrenal axis and the sympathetic nervous system leading to production of interleukins and TNF-α. [10,17]

Increasing serum levels of cytokines after anesthesia, especially GA, is necessary to initiate tissue repair. Therefore, anesthesia and surgical trauma shift the balance of serum cytokines towards proinflammatory factors leads to increased levels of interleukins and TNF-α. However, inflammatory response induced by immune cells may increase the emerging post-surgical complications such as impaired wound healing, systemic inflammatory response and severe hemodynamic disorder, and multiple organ failure. It seems that spinal anesthesia tended to induce lower inflammatory response. [18-20]

Bachmann et al.[21] inflammatory predictors such as IL-1, IL-2 and IL-10 may provide diagnostic contribution with a low error rate for inexperienced physicians and surgeons. It has been stated that serum levels of these predictors increase significantly in complicated appendicitis, whereas less of an increase occurs in serum levels of IL-6 and L-8. [22] Also, IL-6 and IL-8 levels see greater increase secondary to perioperative trauma. [21]

Serum levels of IL-6 were analyzed in the present study because of this response of these cytokines to stress such as surgical trauma.

It has been observed that anesthetic management may have varying influences on postoperative immune response. It has been reported that balanced inhalation anesthesia produced more pronounced alterations in postoperative inflammatory response (IL-6) and cell-mediated immunity than total intravenous anesthesia in patients undergoing elective minimal invasive partial diskectomy. [23, 24]

Some other authors reported that IL-6 response to surgery reflects the extent of tissue damage (Chuickshank et al. 1990) and is decreased when surgery is undertaken with laparoscopic technique (Joris et al. 1992). In addition, the anesthetic management may alter the postoperative IL-6 production [25]

As in the literature, the present study also found that the difference in serum IL- 6 levels tested preoperatively between Group R patients (1.88 ± 0.997 pg/mL) and Group G patients (2.48 ± 0.908 pg/mL) was low and statistically insignificant (p=0.017). The serum IL-6 levels tested at postoperative 12th hour in both groups (7.82 ± 5.149 pg/mL in Group R and 34.73 ± 11.505 pg/mL in Group G) were statistically significant, more so in Group G than Group R (p<0.001).

Clinical Implications:

The elevated IL-6 levels in the GA group could have several clinical implications:

1. Higher IL-6 levels indicate a more significant inflammatory response, which can lead to increased postoperative pain, delayed recovery, and higher risk of complications.
2. The stress-induced cytokine surge in the GA group might affect immune function, potentially impacting wound healing and increasing susceptibility to infections.
3. The controlled IL-6 response in the RA group suggests a potentially smoother postoperative course with reduced inflammation and faster recovery.

Clearly, future studies are necessary to further our understanding about the implications of inflammatory response to anaesthesia.

Limitations In Our Study:

1. Evaluation of IL-6 levels was done only up to 12hours after surgery.
2. Only IL-6 levels were measured ignoring the vast number of other cytokines involved in the immune response.

CONCLUSION

- No significant difference was found between preoperative and postoperative levels of IL-6 in Group R (p<0.05).
- A statistically significant difference was found when comparing preoperative and postoperative serums IL-6 levels in Group G patients (p<0.001).
- When postoperative serum levels were analyzed, IL-6 levels were higher in Group G than in Group R (p<0.001).
- A positive correlation was observed between Group G and Group R (r=0.45; p<0.001).

These findings advocate for the consideration of RA as a preferred anaesthetic technique, particularly in patients where minimizing the inflammatory response is crucial.

Future studies could further explore the efficacy of various anaesthetic techniques like Combined General Anesthesia with Epidural Anaesthesia and Multi-modal Analgesia in suppressing systemic inflammatory response & investigate the rise in other inflammatory markers, such as tumor necrosis factor-alpha (TNF-a), interleukin-10 (IL-10), etc that contribute to the differential impact of GA and RA on the inflammatory response to surgery.

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