Abstract

Anesthesia is an effective way to control stress response. Surgical injury, different anesthesia techniques, and related drugs can directly or indirectly affect the immune system. The perioperative immunosuppression observed in surgical patients is associated with the neuroendocrine stress exerted through the activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis. Dysregulation of this inflammatory process may increase susceptibility to infections and result in postoperative complications, such as wound-healing disturbances and infections leading to sepsis. In this case report which enrolled six patients who underwent femoral bone surgery, three patients were under general anesthesia and three patients were under regional anesthesia. We found that increased neutrophil count and serum C-reactive protein (CRP) concentration were lower in patients under spinal anesthesia compared to those under general anesthesia. In conclusion, the inflammatory response to surgery, which could be seen in the neutrophil count and CRP level, was suppressed during spinal anesthesia to a greater extent than during general anesthesia.

Keywords: C-reactive protein, general anesthesia, neutrophil count, regional anesthesia

Introduction

Surgical injury stimulates the systemic inflammatory response. Different anesthetic techniques for surgery may have an impact on the postoperative systemic inflammatory response and the rate of postoperative infective complications. Anesthetic agents may have both direct and hormone-mediated effects on immune mechanisms, although it may be that the long-term nonspecific hormonal effects of the stress response to anesthesia and surgery may have far more profound implications.

Surgical stress increases the number of T-helper-2 (Th2) cells and decreases the number of T-helper-1 (Th1) cells, resulting in suppressed cell-mediated immunity. C-reactive protein (CRP) is an ancient, highly conserved molecule and a member of the pentraxin family of proteins. CRP is secreted by the liver in response to a variety of inflammatory cytokines. Levels of CRP increase rapidly in response to trauma, inflammation, and infection and decrease just as rapidly with the resolution of the condition. Thus, the measurement of CRP is widely used to monitor various inflammatory states. Patients submitted to anesthesia and surgical procedures suffer diverse immunological alterations, which are difficult to determine if they are induced by anesthetic drugs or by surgical procedural stress.

Case Report

We reviewed six patients aged from 18 to 64 years with American Society of Anesthesiologists physical status I–II (ASA I–II), who had femoral bone surgery with two different anesthetic techniques (general and spinal...
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Figure 1: Leukocyte count chart preoperative and 24 h postoperative

Figure 2: Neutrophil count chart preoperative and 24 h postoperative

Figure 3: Serum C-reactive protein chart preoperative and 24 h postoperative

anesthesia). Laboratory examination found no sign of infection or coagulopathy [Figures 1-4]. We examined the preoperative complete blood count, CRP, and visual analog scale (VAS). The VAS, which ranges from 0 (no pain) to 100 (very severe pain) was used to measure pain intensity throughout the preoperative period and 24 h after the surgery. The first blood sample was taken before the premedication was given to the patients [Table 1]. The second blood sample was taken 24 h after the surgery [Table 2].

All patients received similar premedication: intravenous midazolam 0.01 mg/kg and standard ASA monitoring were applied to the patients. In general anesthesia, patients were induced with propofol 2 mg/kg, fentanyl 2 μg/kg, and atracurium 0.5 mg/kg. Intraoperative maintenance of general anesthesia was made using air/O₂ mixture, sevoflurane, fentanyl, and intermittent atracurium. Spinal anesthesia is carried out as per our institution’s procedure. After skin infiltration with lidocaine, the spinal needle is introduced into the skin, angled slightly cephalad. After the penetration of dura–subarachnoid membranes, which is signaled by the free-flowing cerebrospinal fluid, hyperbaric bupivacaine 0.5% 15 mg is administrated intrathecally. Postoperative analgesia was maintained with fentanyl 0.25 μg/kg/h and paracetamol 500 mg every 6 h. The VAS was measured preoperatively and 24 h after the surgery.[6]

**DISCUSSION**

The stress response to surgery is affected by several factors, including the type of surgery and anesthesia, the magnitude of surgical injury, duration of operation, and the degree of postoperative pain. Anesthetic technique may modulate the extent of this response. Research has been conducted to find a “stress-free anesthetic technique” to limit neuroendocrine, inflammatory, and immune responses. Attenuation of the endocrine–metabolic response may reduce the frequency of postoperative complications.[7]

General anesthesia and surgical stress are considered to suppress immunity, presumably by directly affecting the immune system or activating the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. The pathomechanism of the relationship between surgery- and

| Table 1: Characteristics of the patients who underwent general anesthesia |
|------------------------|------------------------|------------------------|
|                        | Patient I              | Patient II             | Patient III            |
| WBC (×10³)             | 6.3                    | 6.9                    | 7.7                    |
| Platelet (×10³)         | 380                    | 240                    | 240                    |
| Neutrophil (%)          | 67.4                   | 90.8                   | 79.8                   |
| CRP (mg/L)              | 6.43                   | 13.02                  | 6.16                   |
| VAS (mm)                | 10                     | 10                     | 10                     |

| Table 2: Characteristics of the patients who underwent spinal anesthesia |
|------------------------|------------------------|------------------------|
|                        | Patient IV             | Patient V              | Patient VI             |
| WBC (×10³)             | 7.6                    | 6.9                    | 6.6                    |
| Platelet (×10³)         | 476                    | 240                    | 240                    |
| Neutrophil (%)          | 57.6                   | 90.8                   | 79.5                   |
| CRP (mg/L)              | 1.57                   | 3.13                   | 1.32                   |
| VAS (mm)                | 10                     | 10                     | 10                     |

WBC: White blood cell, CRP: C-reactive protein, VAS: Visual analog scale, Pre: Preoperative data, 24 h: 24-h postoperative data
anesthesia technique-induced immunosuppression remains unclear. Transient immunosuppression in patients during anesthesia and surgery may cause postoperative infections. In the immunity against pathogens, the processes of nonspecific defense are of particular importance and engage neutrophils as the significant cell type.

When tissue damage occurs, it may cause an increase in leukocyte counts. The highest counts are seen in patients under general anesthesia. Neutrophil responses consist of bone marrow stimulation under the influence of colony-stimulating factors. There are increased release of polymorphs from the bone marrow reserves into the blood, margination of these cells to the walls of blood vessels, diapedesis through the blood vessel wall into the infected or damaged area, and movement to the invading organism with the help of chemotactic agents and eventually phagocytosis.

Fentanyl is known to enhance natural killer (NK) cells’ cytotoxicity and increase NK and cytotoxic (CD8+) cell counts. Some previous studies showed that the administration of fentanyl would attenuate the expression of pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-6, and IL-8 in vitro. Patients who underwent femoral bone surgery and received fentanyl-based anesthesia had a higher level of stress hormone and higher levels of pro-inflammatory cytokines compared with patients who received spinal anesthesia.

Cho et al. showed that patients who received propofol–remifentanil anesthesia and postoperative ketorolac analgesia exhibited preserved NK-cell cytotoxicity compared with those who received sevoflurane–remifentanil anesthesia and postoperative fentanyl analgesia. The changes in the total leukocyte, neutrophil, and lymphocyte counts and neutrophil-to-lymphocyte ratio over time were not significant between the groups. Surgical incision, on the other hand, caused a rise in the total leukocyte count, which was maximal in the samples taken in the 24 h postoperatively. Our study showed that the neutrophil count in patients who underwent femoral bone surgery was lower with spinal anesthesia than with general anesthesia.

Spinal anesthesia penetrating the systemic circulation can exert anti-inflammatory and immunosuppressive effects by mechanisms involving ion channel modulation (but not Na+ influx) and inhibition of Gq proteins of inflammatory cells, that is, phagocytes. Among other functions, the compounds are also able to inhibit phagocytosis and concomitant respiratory burst with increased production of reactive oxygen species (ROS), serving the oxygen-dependent pathogen degradation and constituting the main functional characteristics of phagocytic cells such as neutrophils and monocytes, crucial for host defense.

One study stated that bupivacaine has its inhibitory effects on the ROS production by phagocytic blood cells, that is, neutrophils, with a concomitant decrease of phagocytosis and the expression impairment of surface receptors involved in this process (FcγRII [CD16], CR1 [CD35], and CR3 [CD11b/CD18]). ROS inhibition by spinal anesthesia was suggested to be associated with their physicochemical properties, specifically lipid solubility, and to be time dependent. Interestingly, the enantiomer-specific effects of bupivacaine concerning its influence on the ROS production were also noted, with the S(-) enantiomer displaying significantly less inhibition. On the other hand, S(-) bupivacaine appeared to be more effective in suppressing neutrophil priming.

In patients under spinal anesthesia, we found that there were lower elevated neutrophil counts compared to patients with general anesthesia. We assumed that it was caused by an increase in the release of neutrophils from the bone marrow by inflammatory cytokines in patients under general anesthesia. Meanwhile, spinal anesthesia suppresses neuroendocrine activity linked to surgical procedures with a sympathetic blockade. As a result, while cortisol levels do not change, cytokine production reduces.

CRP is an acute-phase reactant protein produced in response to inflammation or tissue damage. First, postoperative CRP level is an indicator reflecting the invasiveness of a surgical procedure. Second, the elevated CRP level during the postoperative period is known to be closely associated with the increased leukocyte counts, especially neutrophil count, and some major postoperative complications, including infections. In this case, the reports showed that the increased serum CRP concentration 24 h postoperative was lower in those under spinal anesthesia compared to those under general anesthesia. Some previous studies also confirmed that the anesthetic techniques did influence the acute-phase response based on CRP levels at admission, at delivery, and 24 h after surgery.

The VAS score is widely used to measure pain intensity after surgery. From our case series, we can conclude that there were no significant differences between VAS scores in both techniques.

**Conclusion**

The inflammatory response to surgery, which could be seen in the neutrophil count and CRP level, was suppressed during spinal anesthesia to a greater extent than during general anesthesia. However, the mechanism behind this suppression remains unclear.
anesthesia. According to the VAS pain assessment result, spinal anesthesia is superior to general anesthesia when considering patients’ satisfaction, side effects, and early postoperative analgesia management.

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**Conflicts of interest**
There are no conflicts of interest.

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