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Immunomodulatory Effects Of Ultrasound-Guided Combined Femoral And Sciatic Blocks And Total Intravenous Anesthesia In Oncologic Patients Undergoing Lower Limb Surgeries.

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ABSTRACT

Major surgical procedures lead to perioperative immunosuppression. This study aimed to evaluate the influence of ultrasound (US)-guided combined femoral and sciatic blocks (CFSBs) Total intravenous anesthesia(TIVA) on the immune response of oncologic patients undergoing lower limb surgeries. The study included 36patients with lower limb malignancies scheduled for lower limb-sparing surgery. They were randomly divided to receive CFSBs, (US Group, n=18) or Total intravenous anesthesia (TIVA Group, n=18). Pain intensity and levels of IL-6 and IL-10 were assessed postoperatively. If visualanalogue scale (VAS) scores ≥ 4, a dose of morphine 2.5 mg IV was used. In the two groups, IL-6 and IL-10 levels were comparable at baseline and increased significantly 24 hours after surgery. In US group IL-6 was significantly lower and IL-10 significantly higher than TIVA Group ($p < 0.001$, for both). All patients of the US Group were pain-free up to 6 hours postoperatively. VAS score was significantly lower in US Group ($p < 0.001$) at different time intervals. The total morphine consumption in US Group was 6.7±1.9 mg vs. 17.72 ± 1.32 mg in TIVA Group ($p < 0.001$). US-guided combined femoral and sciatic blocks provide effective anesthesia and enhance the patients' immune response by balancing IL-6/IL-10 ratio compared to conventional epidural anesthesia in patients undergoing surgery for lower limb malignancy.

Keywords: femoral block, sciatic block, lower limb cancer, regional anesthesia

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INTRODUCTION

Major surgical procedures and anesthesia itself often lead to perioperative immunosuppression. This immunosuppression is linked to the activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.[1] Surgical stress inhibits innate immunity from the time of incision through the first postoperative day.[2] Surgical stress stimulates hormonal secretion as catecholamines, adrenocorticotropic hormone, and cortisol that has inhibitory effects on immune functions.[3] After major surgery, the main cytokines (CKs) released are IL-1, TNF-α, and IL-6.[4] Initially, IL-1, and TNF-α are released from activated macrophages and monocytes in the damaged tissues. This stimulates the release of more CKs especially IL-6 that is responsible for inducing the acute phase response.[5]This response is then balanced by an anti-inflammatory phase to prevent the excessive activation of the systemic inflammation, mainly through the release of IL-10.[6] The balance between the proinflammatory and the anti-inflammatory cytokines limit the spread of infection, tissue injury and promote tissue healing and repair through their local and systemic effects.[7]

All forms of general anesthesia have been found to modify the immune system by affecting both innate and adaptive immunity.[8–10] Different anesthetic approaches may modulate the stress response, particularly CK activation. Regional anesthesia is found to inhibit the stress response; many studies showed that regional anesthesia might preserve different immunologic indices better than general anesthesia.[11]

Many studies have suggested that impairment of the immune response might increase perioperative morbidity and mortality in susceptible patients (e.g., all cancer patients) due to infection, recurrence, and metastasis of the malignant tumor.[12] In oncological patients, the immune status is often impaired by the malignant disease itself and by chemotherapy when administered preoperatively.[13,14]

This study aimed to evaluate the influence of ultrasound (US)-guided combined femoral and sciatic blocks versus total intravenous anesthesia (TIVA) on the immune response of oncologic patients undergoing lower limb surgeries for malignancies.

PATIENTS AND METHODS

This study was carried out at National Cancer Institute (NCI), Cairo University. The study was approved by the local anesthesia department scientific and ethical committee (Approval no. MD2010014043.3). All patients were informed about the study design and objectives as well as tools and technique. Every patient provided informed written consentbefore enrollment in the study.

Inclusion criteria were patients between 20 and 60 years old with lower limb malignancies with no evidence of distant metastasis scheduled for lower limb-sparing surgery not exceeding two hours. Exclusion criteria included hepatic and renal impairment, diabetes mellitus or other endocrine disorders, obesity (BMI >30 kg/m2), immune disorders or immunosuppressive therapy, steroid treatment in the last six months, bronchial asthma, coagulopathy, cardiac diseases, and infection at the site of block.

Thirty-six patients were randomly divided into two equal groups. US Group (n=18) included patients who received combined sciatic and femoral nerve blocks (CFSBs). TIVA Group (n=18) included patients who received total intravenous anesthesia.

Methods:

The routine preoperative assessment was done to all patients. In the operating room, patients were monitored continuously using ASA standard monitoring (ECG, pulse-oximetry (SaO2), non-invasive blood pressure and capnography). Blood loss was observed every 5 min. An intravenous (IV) access was established with 16-18 G cannula. Preoperative antibiotic prophylaxis, paracetamol 1 gm IV infusion and 30 mg ketorolac intramuscular were given to all patients. All patients received 0.02 mg/kg midazolam intravenously and 100% O2 via face mask (3-4 L/min) for 3 minutes. Intravenous Ringer's lactate solution was administered to replace fluid deficit preoperatively. Portable ultrasound machine, nerve stimulator, and resuscitation equipment and drugs were available.

In the US Group, levobupivacaine 0.5% was used to a maximum total dose of 2.5 mg/kg to avoid systemic local anesthetic toxicity. Dual guidance (combined US and nerve stimulator 1.5 mA) for nerve location lateral aspect of the thigh 1 cm from the lateral edge of the transducer. The needle was inserted in-plane in a lateral-to-medial orientation and advanced toward the femoral nerve. Nerve stimulation was used to confirm the location of needle tip and passage of the needle through the fascia iliaca. Contact of the needle tip with the femoral nerve was associated with a motor response of the quadriceps muscle group. Once the needle tip was seen, and after careful aspiration, 1-2 mL of glucose 5% was injected to confirm the proper needle placement. A single injection of 15 to 20 mL of levobupivacaine 0.5% was done.

In TIVA group, anesthesia was induced with propofol 2 mg/kg, fentanyl 2 μg/kg and rocuronium 0.6 mg/kg for tracheal intubation. Anesthesia was maintained with continuous infusion of propofol 3-6 mg/kg/hr, fentanyl 1.5-2.5 μg/kg/hr and rocuronium 0.15 mg/kg/hr. Fentanyl was administrated in increments 0.5 μg/kg guided by hemodynamic and clinical requirements (if more than 20% of standard heart rate and blood pressure) .

For postoperative analgesia, all patients received ketorolac 30 mg/12 hrs and IV paracetamol (15 mg/kg) every 8 hours. In case of pain with visualanalogue score (VAS) ≥ 4 a dose of morphine 2.5 mg IV was used.

In the two groups, the pain intensity was assessed using VAS score immediately postoperative and at 1, 2, 6, 12 and 24h postoperative. The total morphine consumption was calculated. For patients and surgeons satisfaction assessment, the following rating scale was reported preoperatively and at 24 hrs postoperative: 1 poor, 2 fair, 3 good, 4 very good and 5excellent.15

Two venous samples were drawn from each patient: prior to anesthesia induction (once intravenous cannula was inserted) (T0) and 24 hours postoperative (T24). Laboratory assay of IL-6 and IL-10 procedure followed the basic principle of sandwich ELISA technique. Commercial kits were supplied by Assaypro, USA (El1006-1) for IL-6 and (El3010-1) for IL-10.

The sample size was calculated based on the findings of Davies et al.16that the estimated mean pain score was 55 in the TIVA group and 40 in US group, with a standard deviation of around 15, at 24 hours post-surgery. The calculated the sample size with alpha 0.05 and power of 80% was 18 patients in each group.

Statistical Methods:

Data management and analysis will be performed using the Statistical Package for Social Sciences (SPSS) vs. 21. Numerical data will be summarized using means and standard deviations or medians and ranges. Categorical data will be summarized as percentages. Comparison of numerical variables between the two groups wasmade using t-test or Mann-Whitney test as appropriate.Comparison between categorical data was performed by the Chi-square or Fisher's exact test. All tests were two-sided. A p-value< 0.05 was considered statistically significant.

RESULTS

Table (1) shows that there was no significant difference between the two groups in age (p = 0.574), sex (p = 0.738), body mass index (p = 0.871), and ASA class (p = 0.738).

Before induction of anesthesia, the levels of IL-6 and IL-10 were comparable in the two groups (Table 2). After 24 hours the two interleukins increased significantly in the two groups. US group has significantly lower IL-6 after and significantly higher IL-10 after 24 hours (p < 0.001, for both).

All patients of the US Group were pain-free up to 6 hours postoperatively. Immediately in PACU, patients of TIVA Group started to experience pain with various degrees (Table 3). At all times of estimations, pain VAS score was significantly lower in US Group (p < 0.001). All patients of TIVA Group were in need of morphine rescue analgesia during the postoperative period compared to 10 patients of the US Group. The total morphine consumption in the ten patients of US Group was 6.7±1.9 mg vs. 17.72 ± 1.32 mg in TIVA Group (p < 0.001).

After Induction of anesthesia (complete block in US Group), mean arterial pressure (MAP) decreased significantly in the US Group and increased significantly in the TIVA Group (Figure 1). It was significantly lower in the US Group (p < 0.001). After that, MAP started to regain the baseline values in the two groups. Similar changes were recorded in heart rate (Figure 2). However, all readings were within the clinically accepted ranges.

Table 1: Baseline characteristics of the two studied groups

	US Group n=18	TIVA Group n=18	p-value
Age (years)	44.1±6.9	43.89±7.24	0.574
Sex (M/F)	9/9	8/10	0.738
Body mass index (kg/m2)	26.4±3.3	27.23 ±2.6	0.871
ASA Class (I/II)	10/8	8/10	0.738

Data are presented as mean±SD or number of patients

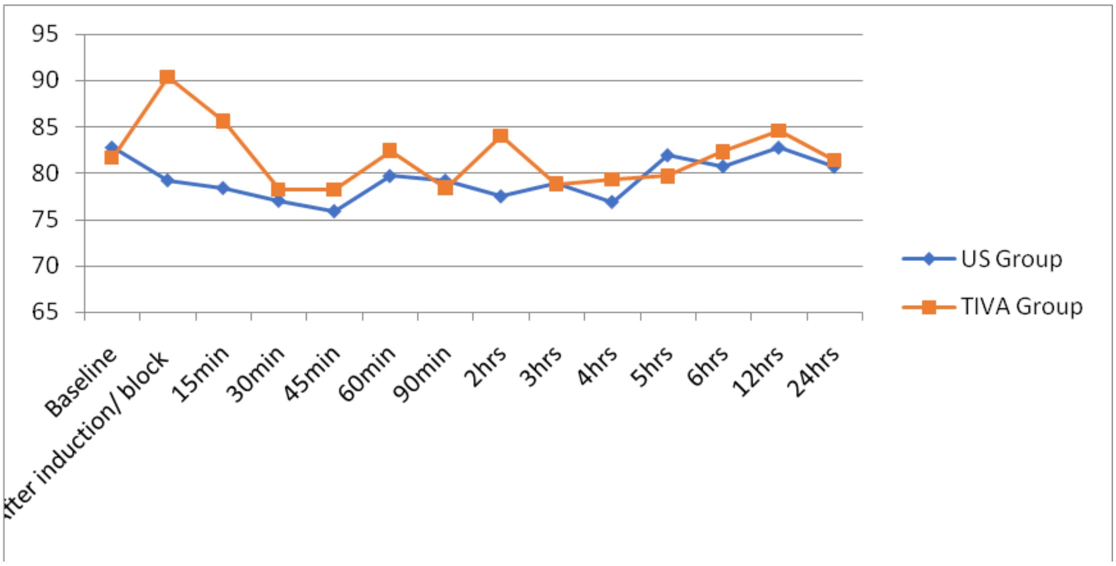
Table 2: Levels of interleukins in the two studied groups before induction of anesthesia and 24 hours postoperatively

	US Group n=18	TIVA Group n=18	p-value
Interleukin-6 (pg/mL)			
Before Induction			
Mean±SD	12.1±5.3	11.1±2.9	0.428
Range	7.7-29.7	7.3-17.3	
Postoperative			
Mean±SD	13.9±5.5	47.8± 10.9	< 0.001
Range	8.2-30.6	42.8-55.3	
p value*	0.012	< 0.001	
Interleukin-10 (pg/mL)			
Before Induction			
Mean±SD	11.5±6.0	10.4±2.6	0.457
Range	7.1-32.1	7.2-14.6	
Postoperative			
Mean±SD	45.6±10.1	15.1± 9.02	< 0.001
Range	18.2-62.7	7.6-45.5	
p value*	< 0.001	0.019	

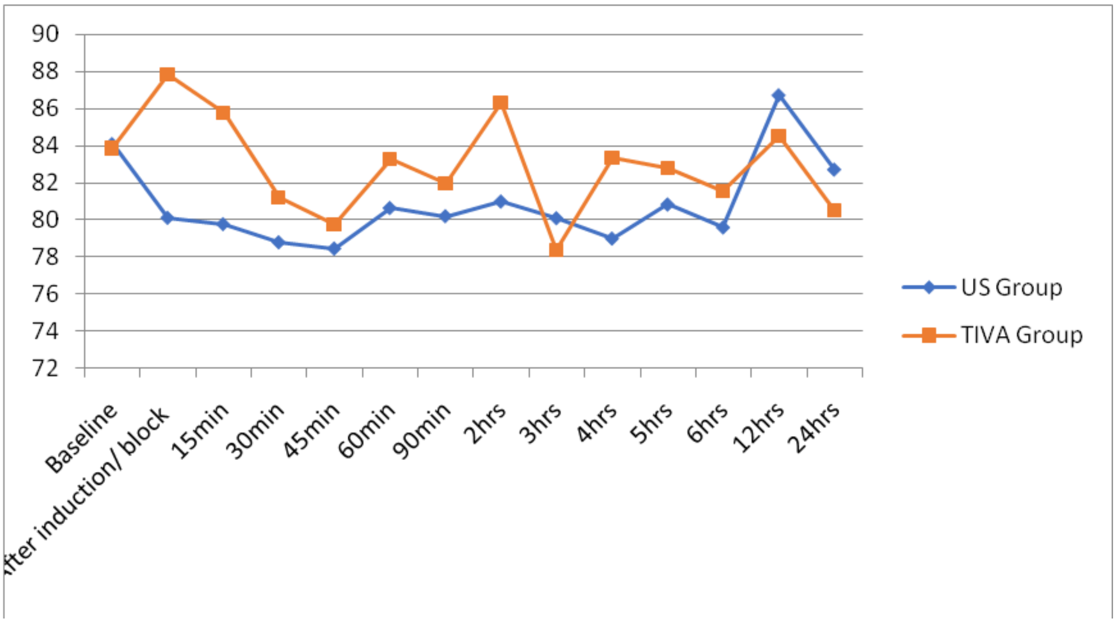
Table 3: VAS pain scores in the two groups during the postoperative period

	US Group n=18	TIVA Group n=18	p-value
In PACU	0 (0-0)	4.5(4-5)	< 0.001
After 1 hr	0 (0-0)	3(2-4)	< 0.001
After 2 hr	0 (0-0)	3(2-3)	< 0.001
After 6 hr	0 (0-0)	4.5(4-5)	< 0.001
After 12 hr	2 (2-3)	4.5(4-5)	< 0.001
After 24 hr	2 (2-3)	4(4-5)	< 0.001

Data are presented as median (range)



Heart rate (beat/min) in the two studied groups in pre-determined time intervals



Mean arterial blood pressure (mmHg) in the three studied groups in pre-determined time intervals.

DISCUSSION

The results of this study demonstrated that IL-6 increased in both groups 24 hours after surgery, but the increase was more marked in the TIVA Group compared to the US Group; the levels of IL-6 increased almost 4-fold after surgery in TIVA Group. On the other hand, IL-10 increase was more marked in the US Group compared to the TIVA Group; it increased almost 4-fold. Therefore, ultrasound-guided combined femoral and sciatic blocks (CFSBs) were better than total intravenous anesthesia in maintaining the immunological balance between IL-6 and IL-10.

It was demonstrated that the immune response to surgical trauma begins with the release of proinflammatory CKs; the acute phase response mediated mainly by IL-6. Then, this response is balanced by an anti-inflammatory phase to prevent the excessive activation of the systemic inflammation.6 The most important anti-inflammatory CK is IL-10.17

Previous studies suggested that regional anesthesia can attenuate the patients' anesthetic and surgical stress compared to general anesthesia.

Moselli et al.18 demonstrated the immunological superiority of regional anesthesia compared to general anesthesia in patients undergoing major surgery for colon cancer. In their series, Epidural anesthesia (as a type of regional anesthesia) attenuates the IL-6 production and the surgery-induced proinflammatory response, while the levels of IL-4 and IL-10 were significantly elevated. Similar findings were reported in comparing spinal anesthesia and intravenous anesthesia.19 Also, preemptive epidural analgesia limited the pro-inflammatory response to surgery in women undergoing elective laparoscopic radical hysterectomy for cervical cancer.20 In patients undergoing primary total knee arthroplasty, a combination of continuous lumbar plexus and sciatic nerve blocks was associated with attenuated postoperative inflammatory response.21 Also, Davies et al. used Epidural anesthesia and CFSBs as perioperative analgesia for knee arthroplasty. Total morphine consumption was lower in CFSBs group.16

Wiryana et al. reported that regional anaesthesia (combined spinal epidural technique) had a superior effect of reducing inflammatory response compared to TIVA by suppressing level of IL6.22 In detecting the inflammatory cytokine expression levels in peripheral blood of patients with cervical discogenic pain before and after cervical nerve block, Bai-shan et al.found that peripheral blood inflammatory cytokines TNF-α, IL-1, IL-6 levels decreased at 24 hours and three days after cervical nerve block therapy compared with before nerve block.23

The safety and efficacy of CFSBs have been previously studied in comparison to neuraxial blocks and general anesthesia. In trauma patients, CFSBs provided adequate anesthesia for an average of 5 hours.24 Ultrasound-guided CFSBs were successful alternative anesthesia method in a group of patients undergoing total knee arthroplasty.25 Also, CFSBs provided adequate anesthesia with sufficient duration in patients undergoing knee arthroscopy.26,27 In these patients, it provided faster bladder function recovery and faster discharging from hospital.28 It was used effectively for above-knee amputations with cardiovascular stability and good postoperative analgesia.29

These effects appear to transient and may be of minor importance in subjects with a healthy immune system. However, in patients with immune dysfunction, multiple organ failure, or other high-risk groups as cancer patients, the influence of anesthetics on the perioperative inflammatory response may have clinical implications.1

In the current study, we compared one type of regional anesthesia; combined femoral and sciatic blocks with general anesthesia (TIVA). We proposed that US-guided CFSBs may enhance the patient's immune response by achieving a balance between the proinflammatory and anti-inflammatory CKs; IL-6 and IL-10 better than conventional TIVA. This expectation was based on possible more patients' comfort, more extended postoperative analgesia, lower morphine consumption, and more attenuation of neuroendocrinal stress response with CFSBs. This technique has gained popularity for lower limb surgeries compared to other anesthetic modalities. The dual guidance using ultrasound and peripheral nerve stimulator (PNS) offers more accurate nerve location and consequently more precise deposition of the local anesthetic solution.30

Concerning the VAS score at PACU, it was significantly higher in TIVA Group than US Group ($P<0.001$). That may be due to short duration of action of last dose fentanyl (first dose morphine was required at PACU) . However, VAS score was significantly higher in TIVA Group than US Group ($P<0.001$) at all recorded times, it may be due to prolonged effect of analgesia in US Group and better pain control by NSAIDS and paracetamol.

Therefore, the 24 hrs morphine consumption postoperative was significantly higher in the TIVA Group than in US Groups ($p<0.001$) at all recorded times. The18 patients in the TIVA Group needed morphine as post operative rescue analgesia when VAS score ≥ 4 while in the US Group only 10 patients required morphine.

In conclusion, US-guided combined femoral and sciatic blocks provide effective unilateral anesthesia in patients undergoing surgery for lower limb malignancy. This technique enhances the patients' immune response by achieving a balance between the proinflammatory cytokine IL-6 and the anti-inflammatory cytokine IL-10 compared to the conventional intravenous anesthesia. It is characterized by hemodynamic stability, high surgeon and patient satisfaction, and low complications rate. Therefore, US-guided combined femoral and sciatic blocks can be a better anesthetic alternative for lower limb surgeries in patients with malignancies or multiple medical co-morbidities.

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