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Effect of interscalene nerve block on the inflammatory response in shoulder surgery: a randomized trial

Gabriel Enrique Mejía-Terrazas, MD, MSc[a,*], Michell Ruíz-Suárez, MD, MSc[b], Felipe Vadillo-Ortega, MD, MSc, PhD[c], Rebecca Elizabeth Franco y Bourland, PhD[d], Eunice López-Muñoz, MD, MSc, PhD[e]

[a]*Anesthesiology Service and Pain Clinic, Hospital Ángeles México, Mexico City, Mexico*
[b]*Traumatology Service, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra," Mexico City, Mexico*
[c]*Unit of Vinculation, Faculty of Medicine, Universidad Nacional Autónoma de México and Laboratory of Metabolism and Nutrition in Experimental Medicine, Instituto Nacional de Medicina Genómica, Mexico City, Mexico*
[d]*Biochemistry Service, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra," Mexico City, Mexico*
[e]*Medical Research Unit in Reproductive Medicine, Unidad Médica de Alta Especialidad, Hospital de Gineco Obstetricia No. 4, "Luis Castelazo Ayala," Instituto Mexicano del Seguro Social, Mexico City, Mexico*

Background: Comparing techniques of general anesthesia and regional anesthesia in arthroscopic shoulder surgery, some studies have shown differences in the intensity of immediate postoperative pain and neuroendocrine response, but the inflammatory response when using balanced general anesthesia (BGA) vs. an ultrasound-guided (USG) single-dose interscalene block (SDIB) has not been compared.
Materials and methods: In a single-center, prospective, randomized clinical trial, the inflammatory response of 2 groups of 10 patients scheduled to undergo arthroscopic shoulder surgery was evaluated through measurement of a panel of cytokines that act on cells of the adaptive immune response to promote or inhibit inflammation, chemokines involved in chemotaxis, the erythrocyte sedimentation rate (ESR), the high-sensitivity C-reactive protein (CRP) level, and the white blood cell (WBC) count in 3 blood samples (before anesthesia, immediately postoperatively, and 24 hours postoperatively) with 2 types of anesthesia (BGA vs. USG SDIB). Postoperative pain intensity (immediately, at 12 hours, and at 24 hours) was also assessed.
Results: The ESR and CRP level increased significantly at 24 hours after surgery; however, the increase in ESR ($P < .0001$) and CRP level ($P < .0001$) was lower in the USG SDIB group. Significant increases in the levels of soluble interleukin 2 receptor α ($P = .022$) and interleukin 12p40 ($P = .016$) occurred in the immediate postoperative period in the USG SDIB group. Immediate postoperative pain showed a significant increase ($P < .001$) in the BGA group.

This study was approved by the local research and ethics committee (Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra," Mexico City, Mexico; registration No. 38/13) and by Registro Brasileiro de Ensaios Clínicos (http://www.ensaiosclinicos.gov.br; registration no. RBR-8bn3y2).

*Reprint requests: Gabriel Enrique Mejía-Terrazas, MD, MSc, Anesthesiology Service and Clinic Pain, Hospital Ángeles México, Tower B, Office 801, Agrarismo 208, Colonia Escandón, Alcaldía Miguel Hidalgo, CP 11800, Mexico City, Mexico.
E-mail address: gisibyg@yahoo.com.mx (G.E. Mejía-Terrazas).

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Conclusions: In arthroscopic shoulder surgery, the use of a USG SDIB compared with the use of BGA is possibly associated with improved pain control in the immediate postoperative period and lower immunosuppression, even at 24 hours after surgery.
Level of evidence: Level I; Randomized Controlled Trial; Treatment Study

Keywords: Interscalene nerve block; balanced general anesthesia; inflammatory response; shoulder surgery; arthroscopic shoulder surgery; postoperative pain

Arthroscopic surgery is one of the most accepted orthopedic therapeutic procedures for a wide variety of shoulder pathologies.[12] This approach allows optimal surgical visibility with less aggression to the capsular structures and the periarticular muscles, as well as minimal soft-tissue trauma. However, despite being a minimally invasive procedure compared with open shoulder surgery, it has been associated with immediate postoperative pain.[23,42,43,49] In this sense, anesthesia—given its potential benefits, such as reduction of the inflammatory response and the intensity of postoperative pain—has acquired a transcendental role in the management of patients undergoing orthopedic surgery. There is evidence of the effects of regional anesthesia on the neuroendocrine response on the functions of immune cells, on gene expression, and on the secretion of inflammatory mediators including cytokines, with considerable advantages over general anesthesia in various surgical procedures.[11,20,27,37] One strategy of regional anesthesia that has recently been used for pain control and reduction in opioid consumption in patients undergoing shoulder surgery is the interscalene block,[22,24,25] with a greater analgesic effect and safety when ultrasound guided (USG).[15,24,41] However, to our knowledge, there are no reports of studies evaluating the effect of an interscalene block on the systemic inflammatory response in arthroscopic shoulder surgery. The purpose of this study was to evaluate the inflammatory response in 3 blood samples (before anesthesia, immediately postoperatively, and 24 hours postoperatively) in patients undergoing arthroscopic shoulder surgery under balanced general anesthesia (BGA) vs. a USG single-dose interscalene block (SDIB).

Materials and methods

We performed a single-center, prospective, randomized clinical trial. Patients aged 35 to 70 years who were scheduled to undergo arthroscopic surgery on the shoulder and had an American Society of Anesthesiologists physical status classification of I or II were included in the study. To avoid local or systemic cofactors and cointerventions such as drugs that could modify or influence the systemic inflammatory response, the exclusion criteria were as follows: obesity (body mass index > 30 kg/m^2), malnutrition, diabetes mellitus, metabolic syndrome, pre-existing coagulopathy, acute or chronic focus of infection, congenital or acquired immunologic disease, collagen disease, local or systemic inflammatory disease, endocrine disease, oncologic disease, psychiatric illness, organ failure, chronic pain in another bodily region, use of steroids or immunomodulators, chronic use of nonsteroidal anti-inflammatory drugs, chronic use of α_2-adrenergic agonists, previous surgery on the same shoulder, airway difficulties, and presurgical leukocyte count less than 4×10^3/mm^3 or greater than 11×10^3/mm^3.

Written informed consent was obtained from each patient. During the preoperative visit, all patients were instructed on using the visual analog scale, with 0 representing absence of pain and 10 representing the worst pain imaginable.[18] Patients were randomly assigned to the BGA group or the USG SDIB group by use of a computer-generated random number in a 1:1 relation (www.Random.org). Allocation numbers were saved on an opaque sheet that was folded and stapled, which was consulted immediately before surgery by an independent anesthesiologist who was not involved in the assessment of outcomes. Outcome assessors and data analyzers were blinded to the treatment allocation.

Each patient was monitored using standard protocols (noninvasive monitoring of blood pressure in the contralateral arm, electrocardiography, pulse oximetry, and temperature) every 5 minutes during surgery. A nurse recorded the side effects of anesthesia management and surgery. Patients were eliminated from the study if they required a change in anesthetic technique; required use of nonsteroidal anti-inflammatory drugs and surgical reintervention; had severe hypothermia, fever, and toxicity due to local anesthetics; had allergic reactions; or withdrew consent.

All anesthesiology procedures were performed by an anesthesiologist with more than 5 years of experience in both techniques. BGA was induced with fentanyl at 3 μg/kg, cisatracurium besylate at 0.15 mg/kg, and propofol at 1.5 mg/kg administered intravenously. All patients received orotracheal intubation under direct laryngoscopy in 1 attempt with a high-volume low-pressure balloon endotracheal catheter with a Murphy-type orifice (Covidien; Medtronic, Dublin, Ireland) of 7.5 to 8 mm. Anesthesia was maintained with 1 minimum alveolar concentration of desflurane.

The USG SDIB was performed under sedation with midazolam at 0.4 mg/kg and fentanyl at 1 μg/kg. A 6-cm, 6- to 15-MHz ultrasound transducer probe (MicroMaxx L25; SonoSite, Bothell, WA, USA) was used. The ultrasound transducer was initially placed on the supraclavicular fossa to locate the supraclavicular brachial plexus, which was shown as a hypoechoic bundle lateral and superficial to the subclavian artery. By moving the transducer cranially, the brachial plexus was revealed between the anterior and middle scalene muscle. An ultrasound reflector-coated nerve block needle (22-gauge, 50-mm short-bevel needle [Stimuplex D; B. Braun, Melsungen, Germany]) connected to a peripheral nerve stimulator (Stimuplex DIG RC; B. Braun) with an out-of-plane approach was introduced into the plexus sheath under ultrasound guidance and placed between the C5 and C6 nerve roots. The stimulator settings were as follows: 0.5 mA with an impulse time

duration of 0.1 milliseconds and impulse frequency of 2 Hz.[14,42] The needle position was confirmed by activation of the deltoid motor reflex with a current output of 0.5 mA. After aspiration to exclude intravascular injection, 2 mg/kg of 0.75% ropivacaine and 3 mg/kg of 2% lidocaine solution with a 30-mL maximum were injected. Oxygen was applied at a flow rate of 6 L/min via an oxygen mask.

The postoperative analgesia protocol for both groups included intravenous administration of 1 g of paracetamol (acetaminophen) and 100 mg of tramadol every 8 hours. When the postoperative pain score was greater than 5, we administered 5 mg of morphine intravenously every 8 hours.

Operative technique

A single surgeon performed the arthroscopic procedures, and all operations were performed with patients in the beach-chair position. Four types of surgical procedures were performed: rotator cuff repair (arthroscopically or mini-open repair technique), selective anterior capsulotomy, suture anchor repair, and subacromial decompression.

Outcome measures

With a minimum fasting period of 8 hours, quantification of interleukin (IL) 1α, IL-1β, IL-2, IL-6, IL-10, IL-12p40, IL-17, IL-1 receptor antagonist, soluble IL-2 receptor α (sIL-2RA), interferon gamma–induced protein 10 kDa (IP-10), monocyte chemoattractant protein 1, macrophage inflammatory protein (MIP) 1α, MIP-1β, tumor necrosis factor (TNF) α, vascular endothelial growth factor (VEGF), eotaxin, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (CRP) level, and white blood cell (WBC) count was performed for each patient from 9 mL of venous blood on 3 occasions: before anesthesia, immediately postoperatively, and 24 hours postoperatively. The cytokine and CRP levels were quantified in 5 mL of blood placed in BD Vacutainer tubes (code 368175; Becton Dickinson, Franklin Lakes, NJ, USA), with transparent plastic (13 × 100 mm, 6.0 mL), without an anticoagulant, with a coagulation activator, with a red Hemogard safety cap (Becton Dickinson). Hemolyzed, icteric, or lipemic samples were discarded. The blood samples were centrifuged within 30 minutes after collection at 1100 rpm for 10 minutes. The serum was separated into aliquots of 500 μL in polypropylene tubes (600 μL). Serum aliquots were placed at −20°C for 2 hours and subsequently stored at −80°C until analysis. Quantification of cytokines was performed by a multiplex assay using the High Sensitivity Human Cytokine Magnetic Bead kit (Millipore, Burlington, MA, USA). The plates were prepared according to the manufacturer's instructions. In brief, each plate was blocked with wash buffer for 10 minutes before use. The mixed beads were placed into each well and washed twice. Reconstitution of the high-sensitivity human cytokine standard, according to the manufacturer's instructions, with serial 1:5 dilutions for a working concentration range of 10 to 10,000 pg/mL, generated the standard curve. The samples and standards were incubated with the mixed beads overnight at 4°C while being shaken. The beads were washed and then incubated with a detection antibody at room temperature for 1 hour and with streptavidin for an additional 30 minutes. The beads were washed twice and resuspended in MagPix drive fluid (Millipore), and the plate was analyzed on the MagPix plate reader (Millipore). The mean fluorescence intensity was compared with the standard curve to calculate the cytokine concentration in picograms per milliliter. Each standard curve was then individually analyzed for outliers and adjusted as necessary to achieve linearity ($R^2 \geq 0.8$). The mean fluorescence intensity values were adjusted for the background.

The CRP level was determined by means of chemiluminescence with the Immulite 1000 Immunoassay System (Siemens Healthcare Diagnostics, Hoffman Estates, IL, USA), with a detection range of 0.1 to 100 mg/L. The interassay variation coefficients were less than 10%.

The ESR and WBC count were quantified in 4 mL of blood that was placed in BD Vacutainer tubes with EDTA K2 (code 367844; Becton Dickinson), with transparent plastic (13 × 75 mm, 4.0 mL) and a lilac Hemogard safety cap (Becton Dickinson). Quantification of the ESR using the Wintrobe method was carried out within 30 minutes after the extraction of the sample.[50] In brief, the sample was homogenized, avoiding the formation of bubbles; then, with a Pasteur pipette, the Wintrobe tube (scale from 0 to 10 cm, divided into millimeters) was filled to the mark, avoiding the formation of bubbles and keeping the tube in a 90° position with respect to the surface, free of vibrations. The tube was placed in the Wintrobe rack and allowed to stand in place without movement or vibrations, and after exactly 60 minutes, the distance between the upper edge of the plasma and the base of the cells was recorded (in millimeters per hour). Quantification of the WBC was carried out in a computerized hemo-analyzer using the electrical impedance method (Coulter LH 780 Hematology Systems; Beckman Coulter, Brea, CA, USA) with the results provided automatically by the equipment.

Assessments of the presence and intensity of postoperative pain were performed 3 times (immediately, 12 hours, and 24 hours postoperatively). The intensity of pain was evaluated with a visual analog scale with a 10-cm horizontal line anchored by 2 verbal descriptors at each end, where 0 indicates no pain and 10 indicates the worst possible pain.[18] All pain scores were recorded with a corresponding date and time, as were the start and end times of the related surgical procedure.

Statistical methods

On the basis of studies of the influence of anesthetic techniques on the release of proinflammatory cytokines (TNF, IL-6, and IL-1),[8,20,43] a sample size calculation was performed to compare paired measurements (one at baseline and another after the intervention) in the 2 study groups. The Sample Size Calculator of Statulator[beta] (http://statulator.com/SampleSize/ss2PM.html) was used, taking the expected mean of the paired differences of the baseline and final IL-6 average in each group (15.4 pg/mL) and the expected standard deviation of the paired differences (10.88 pg/mL)[43] with a $1\text{-}\beta$ value of .80 and α level of .05. This estimated that at least 8 patients would be required to demonstrate statistically significant differences. By adding 20% to account for possible losses during the study, a final group size of 10 patients was obtained for each study group.

Data were entered and analyzed using the SPSS computer package (version 22.0; IBM, Armonk, NY, USA). The normality of quantitative variables was tested by the Shapiro-Wilk test. Because of the small sample size and non-normal distribution of most of the

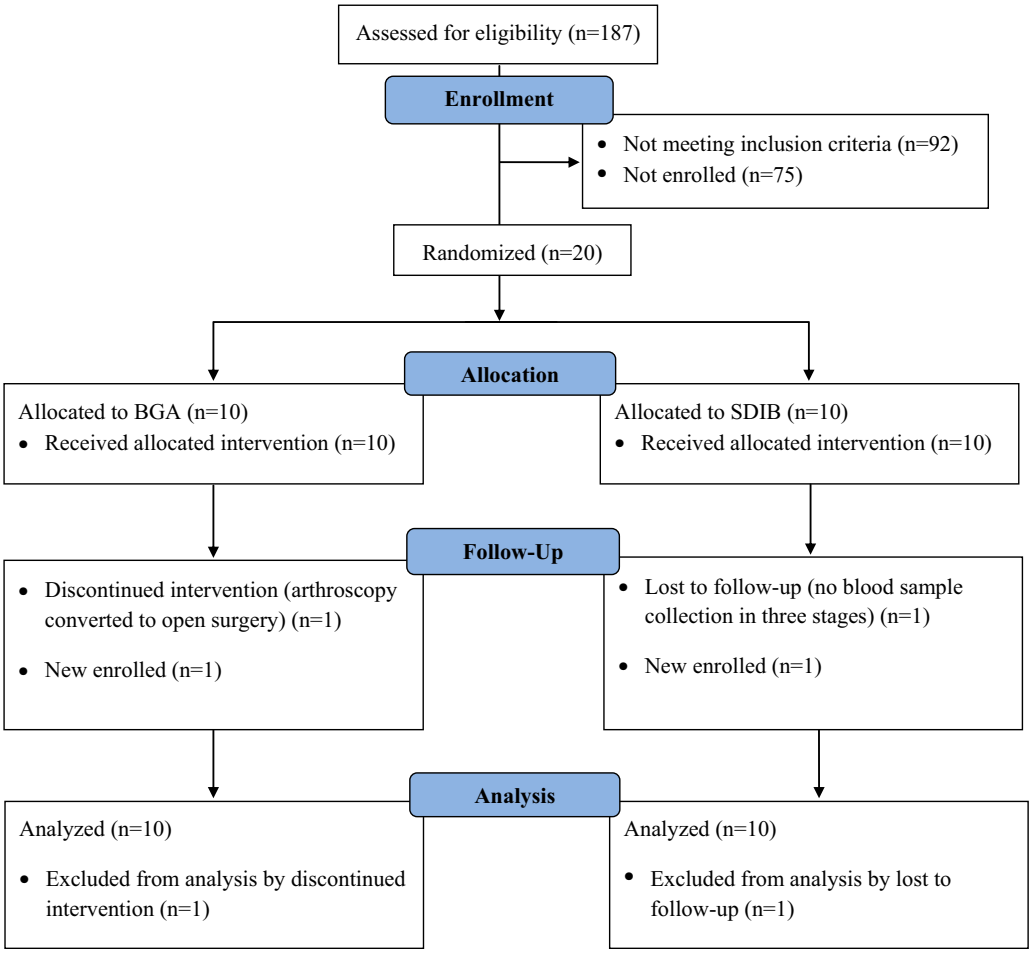

Figure 1 Flow diagram of participants through each stage of randomized trial. *BGA*, balanced general anesthesia; *SDIB*, ultrasound-guided single-dose interscalene block.

variables, nonparametric tests were applied in all comparisons. Between-group differences in clinical variables, cytokine levels, ESRs, CRP levels, and WBC counts were examined by the Mann-Whitney *U* test, whereas within-group differences were examined by the Friedman test. Qualitative variables were expressed as frequencies and percentages and were analyzed using the Fisher exact test. A resampling technique (bootstrapping) was performed with Monte Carlo simulation (99% confidence interval and 10,000 samples) from the available data to construct a sample distribution and contrast the intragroup and between-group differences in all variables.[5,13,32] All tests were 2-tailed, and statistical significance was considered for $P < .05$. Bonferroni correction was performed for multiple comparisons, obtaining an adjusted *P* value of .0004.

Results

Between April and November 2014, 187 patients scheduled for arthroscopic surgery on the shoulder were evaluated and 20 were deemed eligible for the study. Of these, 10 were randomly assigned to the BGA group and 10 were randomly assigned to the USG SDIB group. During the study, 2 losses occurred, 1 in the USG SDIB group owing to a change in surgical technique, in which arthroscopy was converted to open surgery, and 1 in the BGA group, as the blood samples were not collected on all 3 occasions. These losses were not included in the analysis and were replaced by 2 other patients (Fig. 1). Patient demographic profiles and details of the surgical procedures performed are summarized in Table I. Immediate postoperative pain was significantly greater in the BGA group than in the USG SDIB group. No statistical differences were found between the groups in terms of age, sex, body mass index, surgery time, or surgery type.

Detailed results of the assessed hematologic variables in relation to the type of anesthesia are shown in Table II. The ESR, CRP level, and WBC count were significantly increased in the samples taken 24 hours after surgery compared with the samples taken before anesthesia or in the immediate postoperative period. However, the increase in the ESR (in the immediate postoperative period and at 24 hours) and CRP level (in the immediate postoperative period) was significantly lower in the USG SDIB group ($P < .05$ and $P < .0004$) (Fig. 2).

Table I Patient data

Variables	Anesthetic technique		*P* value: exact*	*P* value (95% CI): bootstrapping with Monte Carlo simulation*
	BGA (n = 10)	SDIB (n = 10)		
Age, yr	47.0 (26.5-53.5)	33.5 (22.0-66.5)	.617	.609 (.597-.622)
Sex			>.999	>.999 (>.999 to >.999)
Female	5 (50.0)	5 (50.0)		
Male	5 (50.0)	5 (50.0)		
Weight, kg	70.0 (60.0-76.0)	67.0 (59.0-71.8)	.615	.614 (.602-.627)
Height, cm	166.0 (161.5-172.5)	162.5 (153.0-170.8)	.322	.316 (.304-.328)
Body mass index, kg/m^2	24.7 (22.9-27.8)	25.4 (24.5-25.7)	.810	.811 (.801-.821)
Surgery time, min	80.0 (70.0-87.5)	77.5 (63.0-130.0)	.898	.896 (.888-.904)
Postoperative pain				
Immediately	3.0 (2.0-4.0)	0.0 (0.0-0.0)	<.0001†	<.0001†
12 h	3.0 (2.0-3.0)	2.5 (2.0-3.0)	.450	.455 (.442-.468)
24 h	3.0 (2.0-3.3)	3.0 (2.8-3.3)	.347	.350 (.338-.362)
P value: exact‡	>.999	<.0001†		
P value: bootstrapping with Monte Carlo simulation‡	>.999 (>.999 to >.999)	<.0001†		
Surgical diagnosis			>.999	>.999 (>.999 to >.999)
Rotator cuff injury	5.0 (50.0)	6.0 (60.0)		
Adhesive capsulitis	0.0 (0.0)	1.0 (10.0)		
Glenohumeral instability	4.0 (40.0)	3.0 (30.0)		
Subacromial impingement	1.0 (10.0)	0.0 (0.0)		

BGA, balanced general anesthesia; *SDIB*, single-dose interscalene block; *CI*, confidence interval.
Data are presented as median (interquartile range) or frequency (percentage).
* Significance determined by Mann-Whitney *U* test or Fisher exact test.
† Statistically significant.
‡ Significance determined by Friedman test.

Table II Hematologic variables according to anesthetic technique

	Anesthetic technique		*P* value: exact*	*P* value (95% CI): bootstrapping with Monte Carlo simulation*
	BGA (n = 10)	SDIB (n = 10)		
ESR, mm/h				
Before anesthesia	2.5 (1.0-4.0)	1.0 (0.0-2.0)	.087	.089 (.082-.097)
Immediately postoperatively	34.0 (30.0-50.0)	14.0 (13.0-15.5)	<.0001†	<.0001†
24 h postoperatively	50.5 (38.0-56.3)	25.5 (23.3-27.5)	.001†	<.0001†
P value: exact‡	<.0001†	<.0001†		
P value: bootstrapping with Monte Carlo simulation‡	<.0001†	<.0001†		
CRP level, mg/L				
Before anesthesia	2.5 (1.8-4.3)	2.5 (1.8-3.0)	.748	.755 (.744-.766)
Immediately postoperatively	24.5 (23.0-32.5)	16.0 (14.8-17.0)	<.0001	<.0001†
24 h postoperatively	31.0 (26.8-34.8)	28.5 (27.8-29.0)	.191	.204 (.194-.214)
P value: exact‡	<.0001†	<.0001†		
P value: bootstrapping with Monte Carlo simulation‡	<.0001†	<.0001†		
WBC count, $\times 10^3$/mm^3				
Before anesthesia	6.5 (5.6-6.7)	5.6 (5.4-6.2)	.06	.064 (.058-.070)
Immediately postoperatively	7.1 (6.5-7.8)	6.3 (6.1-6.9)	.066	.067 (.061-.074)
24 h postoperatively	7.8 (7.2-8.6)	7.0 (6.7-7.6)	.06	.063 (.057-.069)
P value: exact‡	<.0001†	<.0001†		
P value: bootstrapping with Monte Carlo simulation‡	<.0001†	<.0001†		

Data are presented as median (interquartile range).
BGA, balanced general anesthesia; *SDIB*, single-dose interscalene block; *CI*, confidence interval; *ESR*, erythrocyte sedimentation rate; *CRP*, high-sensitivity C-reactive protein; *WBC*, white blood cell.
* Significance determined by Mann-Whitney *U* test.
† Statistically significant.
‡ Significance determined by Friedman test.

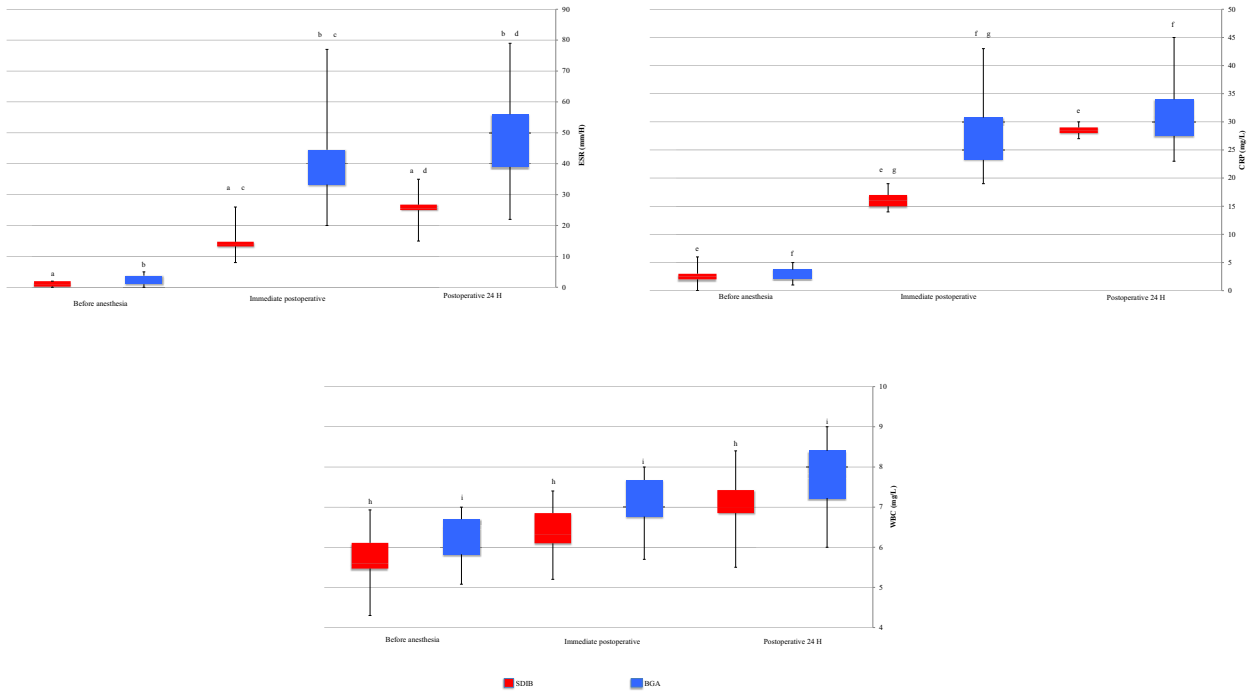

Figure 2 Median and interquartile range of erythrocyte sedimentation rate (*ESR*), high-sensitivity C-reactive protein (*CRP*) level, and white blood cell (*WBC*) count in 3 blood samples (before anesthesia, immediately postoperatively, and 24 hours postoperatively) with 2 types of anesthesia: balanced general anesthesia (*BGA*) vs. ultrasound-guided single-dose interscalene block (*SDIB*). Statistically significant differences ($P < .05$ and $P < .0004$) between pairs are indicated by letters.

The values of IP-10, MIP-1β, TNF-α, and VEGF showed a statistically significant reduction ($P < .05$) in the samples taken 24 hours after surgery compared with the samples taken before anesthesia or in the immediate postoperative period in the BGA group (Fig. 3), even though there were no statistically significant differences in the values of these cytokines in the USG SDIB group or when we compared the BGA group with the USG SDIB group (Table III). The values of sIL-2RA and IL-12p40 showed a statistically significant increase ($P < .05$) in the samples taken in the immediate postoperative period in the USG SDIB group compared with the BGA group (Fig. 4).

Discussion

Under normal conditions, an immunoinflammatory response occurs after surgical procedures with the secretion of cytokines, which function as immunity regulators, limiting the damage or excess of inflammatory reactions.[21,26,28,48,52] The expression and balance of perioperative cytokines can vary depending on the extent of the surgical trauma—and even depending on the type of anesthesia and anesthetic agents used.[11,31,39] Arthroscopic shoulder surgery is used to reduce the extent of surgical trauma, and regional anesthesia techniques are used to modify the response to stress through regulation or inhibition of nociceptive afferent signals in the area of surgical trauma.[11,20,27,37] Drugs used in regional anesthesia, such as ropivacaine and lidocaine, have anti-inflammatory properties, with decreased adherence, migration, and accumulation at the site of polymorphonuclear inflammation and functional modification of macrophages and monocytes.[7] This supports the hypothesis that the effects are related not only to anesthetic technique but also to the type of anesthetic.

As there have been no published reports evaluating the systemic inflammatory response in patients undergoing arthroscopic shoulder surgery under a USG SDIB with ropivacaine and lidocaine compared with BGA, the objective of our study was to evaluate the systemic inflammatory response using these 2 anesthetic methods. The serum levels of cytokines that act on cells of the adaptive immune response, to promote or inhibit inflammation, as well as chemokines involved in chemotaxis,[4,30] were compared. We chose these cytokines and chemokines because deterioration of the immune function related to surgical procedures is initially caused by induction of the acute-phase inflammatory response by macrophages and monocytes, which release proinflammatory cytokines, particularly TNF-α and IL-1β,[4,19,30] which in turn stimulate the production of IL-6. This is a primary effector of the production of acute-phase proteins, such as CRP, involved in both specific and nonspecific immune response and plays an important role in the proliferation of polymorphonuclear progenitor cells in the bone marrow, with an increase in WBC count, particularly

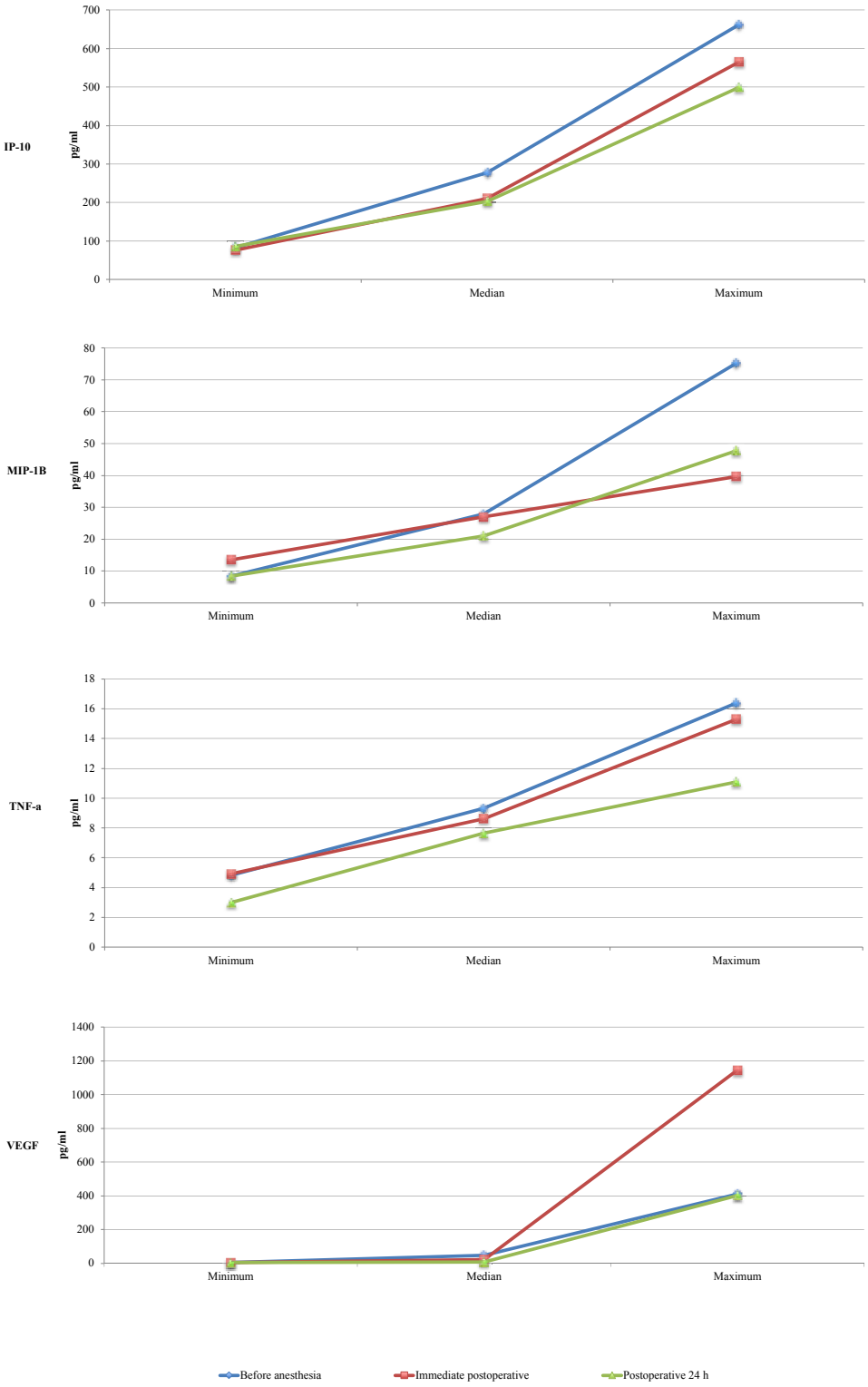

Figure 3 Minimum, median, and maximum levels of interferon gamma–induced protein 10 kDa (*IP-10*), macrophage inflammatory protein 1β (*MIP-1B*), tumor necrosis factor α (*TNF-a*), and vascular endothelial growth factor (*VEGF*) in balanced general anesthesia group. Statistically significant differences ($P < .05$) were found when comparing the three times in which they were evaluated (before anesthesia, immediately postoperatively, and 24 hours postoperatively).

Table III Cytokine values according to anesthetic technique

	Anesthetic technique		*P* value: exact*	*P* value (95% CI): bootstrapping with Monte Carlo simulation*
	BGA (n = 10)	SDIB (n = 10)		
Adaptive immunity				
IL-2, pg/mL				
Before anesthesia	0.98 (0.98-1.08)	0.98 (0.97-10.24)	.896	.893 (.885-.901)
Immediately postoperatively	0.98 (0.98-0.98)	0.98 (0.97-12.91)	.779	.780 (.769-.790)
24 h postoperatively	0.98 (0.98-0.98)	0.98 (0.91-3.71)	.344	.355 (.343-.368)
P value: exact†	.667	.431		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.665 (.662-.677)	.437 (.424-.449)		
Proinflammatory cytokine				
IL-1α, pg/mL				
Before anesthesia	0.11 (0.11-9.88)	12.64 (0.11-24.59)	.305	.315 (.303-.327)
Immediately postoperatively	0.11 (0.11-1.33)	2.12 (0.11-29.86)	.403	.410 (.397-.422)
24 h postoperatively	0.11 (0.11-2.33)	2.97 (0.11-23.77)	.196	.196 (.185-.206)
P value: exact†	.477	.943		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.471 (.458-.484)	.944 (.938-.950)		
IL-1β, pg/mL				
Before anesthesia	0.71 (0.71-0.71)	0.71 (0.71-13.94)	.055	.055 (.049-.061)
Immediately postoperatively	0.71 (0.71-0.71)	0.71 (0.71-24.69)	.055	.055 (.049-.061)
24 h postoperatively	0.71 (0.71-0.71)	0.71 (0.70-3.01)	.160	.162 (.152-.171)
P value: exact†	>.999	.431		
P value (95% CI): bootstrapping with Monte Carlo simulation†	>.999 (>.999 to >.999)	.428 (.415-.441)		
IL-17, pg/mL				
Before anesthesia	1.34 (0.85-6.97)	4.71 (0.61-15.01)	.516	.516 (.503-.529)
Immediately postoperatively	1.13 (0.50-3.66)	4.62 (0.79-10.48)	.197	.206 (.196-.217)
24 h postoperatively	0.82 (0.58-1.50)	2.57 (0.84-9.46)	.171	.173 (.163-.182)
P value: exact†	.056	.897		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.052 (.046-.057)	.902 (.894-.909)		
TNF-α, pg/mL				
Before anesthesia	9.31 (7.55-12.69)	6.52 (4.28-12.33)	.256	.260 (.249-.272)
Immediately postoperatively	8.63 (7.18-9.46)	8.55 (4.29-12.71)	.955	.955 (.949-.960)
24 h postoperatively	7.65 (5.99-8.58)	7.11 (5.12-12.18)	.896	.904 (.896-.911)
P value: exact†	.021‡	.806		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.022 (.018-.026)	.804 (.794-.801)		
Anti-inflammatory cytokine				
IL-1RA, pg/mL				
Before anesthesia	0.51 (0.51-0.54)	0.51 (0.51-37.07)	.235	.239 (.228-.250)
Immediately postoperatively	0.51 (0.51-8.48)	0.51 (0.51-130.06)	.206	.207 (.196-.217)
24 h postoperatively	0.51 (0.51-2.53)	0.51 (0.51-29.28)	.513	.525 (.512-.537)
P value: exact†	.333	.528		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.341 (.329-.354)	.527 (.514-.540)		
sIL-2RA, pg/mL				
Before anesthesia	0.51 (0.51-0.51)	0.51 (0.51-0.51)	.211	.219 (.208-.229)
Immediately postoperatively	0.51 (0.51-0.51)	0.51 (0.51-0.51)	.022‡	.024 (.020-.028)
24 h postoperatively	0.51 (0.51-0.51)	0.51 (0.51-0.51)	.289	.296 (.285-.308)
P value: exact†	.667	>.999		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.670 (.658-.682)	>.999 (>.999 to >.999)		
IL-10, pg/mL				
Before anesthesia	1.07 (1.07-1.07)	1.08 (1.06-4.25)	.724	.725 (.713-.736)

(*continued on next page*)

Table III Cytokine values according to anesthetic technique (*continued*)

	Anesthetic technique		*P* value: exact*	*P* value (95% CI): bootstrapping with Monte Carlo simulation*
	BGA (n = 10)	SDIB (n = 10)		
Immediately postoperatively	1.07 (1.07-1.57)	5.90 (1.09-13.73)	.104	.107 (.099-.115)
24 h postoperatively	1.07 (1.07-1.07)	1.09 (1.06-4.23)	.133	.137 (.128-.146)
P value: exact†	.074	.236		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.077 (.070-.083)	.237 (.226-.248)		
IL-12p40, pg/mL				
Before anesthesia	1.31 (1.31-2.93)	1.31 (1.31-13.48)	.615	.615 (.603-.628)
Immediately postoperatively	1.31 (1.31-1.31)	1.31 (1.31-38.30)	.016‡	.018 (.015-.021)
24 h postoperatively	1.31 (1.31-3.28)	1.31 (1.31-9.84)	.115	.122 (.113-.130)
P value: exact†	.123	.431		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.123 (.114-.131)	.435 (.422-.447)		
Proinflammatory or anti-inflammatory cytokine				
IL-6, pg/mL				
Before anesthesia	0.80 (0.80-1.45)	0.81 (0.80-6.47)	.590	.589 (.577-.602)
Immediately postoperatively	0.80 (0.80-2.00)	1.29 (0.80-7.96)	.362	.356 (.343-.368)
24 h postoperatively	0.88 (0.80-3.43)	1.60 (0.81-7.36)	.669	.672 (.660-.684)
P value: exact†	.221	.680		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.220 (.209-.230)	.672 (.660-.684)		
Chemokine				
IP-10, pg/mL				
Before anesthesia	277.71 (203.44-378.93)	291.97 (245.07-362.78)	.853	.854 (.845-.863)
Immediately postoperatively	210.62 (169.67-344.24)	317.72 (227.05-372.77)	.218	.219 (.208-.230)
24 h postoperatively	203.49 (146.00-257.94)	208.94 (190.88-243.03)	.739	.744 (.733-.756)
P value: exact†	.007‡	.316		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.007 (.005-.009)	.318 (.306-.330)		
MCP-1, pg/mL				
Before anesthesia	366.87 (304.09-476.93)	353.93 (244.20-407.41)	.481	.496 (.483-.509)
Immediately postoperatively	493.45 (300.72-671.40)	369.94 (262.55-493.85)	.315	.320 (.308-.332)
24 h postoperatively	403.32 (299.08-568.05)	320.49 (270.82-662.35)	.481	.496 (.483-.509)
P value: exact†	.710	.974		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.711 (.699-.723)	.974 (.970-.978)		
MIP-1α, pg/mL				
Before anesthesia	3.20 (2.81-4.80)	4.14 (2.81-8.96)	.493	.496 (.483-.509)
Immediately postoperatively	2.81 (2.81-3.19)	2.81 (2.81-11.73)	.324	.319 (.307-.331)
24 h postoperatively	2.81 (2.00-3.37)	2.81 (1.99-6.66)	.541	.538 (.525-.551)
P value: exact†	.522	.140		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.519 (.506-.532)	.142 (.133-.151)		
MIP-1β, pg/mL				
Before anesthesia	27.90 (17.68-41.62)	21.53 (12.99-66.16)	>.999	>.999
Immediately postoperatively	26.98 (19.22-31.04)	29.71 (15.01-58.54)	.739	.744 (.733-.756)
24 h postoperatively	21.01 (14.74-31.04)	23.23 (11.71-63.14)	.869	.876 (.867-.884)
P value: exact†	.012‡	.763		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.012 (.009-.015)	.763 (.752-.774)		
Eotaxin, pg/mL				
Before anesthesia	108.83 (67.96-130.61)	101.04 (68.06-119.43)	.631	.639 (.626-.651)
Immediately postoperatively	84.57 (61.51-124.96)	93.98 (61.87-121.80)	.869	.876 (.867-.884)
24 h postoperatively	62.51 (52.27-114.51)	84.87 (56.99-128.39)	.315	.320 (.308-.332)
P value: exact†	.222	.974		

(*continued on next page*)

Table III Cytokine values according to anesthetic technique (*continued*)

	Anesthetic technique		*P* value: exact*	*P* value (95% CI): bootstrapping with Monte Carlo simulation*
	BGA (n = 10)	SDIB (n = 10)		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.219 (.208-.229)	.976 (.972-.979)		
Proangiogenic growth factor				
VEGF, pg/mL				
Before anesthesia	47.54 (3.11-217.37)	154.59 (3.11-440.54)	.838	.840 (.830-.849)
Immediately postoperatively	20.53 (3.11-97.07)	135.10 (9.26-324.55)	.184	.183 (.173-.-.193)
24 h postoperatively	7.21 (3.11-101.92)	166.28 (3.11-294.23)	.197	.202 (.192-.212)
P value: exact†	.021‡	.967		
P value (95% CI): bootstrapping with Monte Carlo simulation†	.019 (.016-.023)	.967 (.963-.972)		

Data are presented as median (interquartile range).
BGA, balanced general anesthesia; *SDIB*, single-dose interscalene block; *CI*, confidence interval; *IL*, interleukin; *TNF*, tumor necrosis factor; *IL-1RA*, interleukin 1 receptor antagonist; *sIL-2RA*, soluble interleukin 2 receptor α; *IP-10*, interferon gamma–induced protein 10 kDa; *MCP*, monocyte chemoattractant protein; *MIP*, macrophage inflammatory protein; *VEGF*, vascular endothelial growth factor.
* Significance determined by Mann-Whitney *U* test.
† Significance determined by Friedman test.
‡ Statistically significant.

polymorphonuclear progenitor cells in the circulation after surgery.[4,30,35,45] In addition to its proinflammatory activity, IL-6 functions as an immunomodulatory cytokine required to control the acute local or systemic response by increasing glucocorticoid synthesis,[51] which has anti-inflammatory properties.[30] IL-6 also induces macrophages to release prostaglandin E2, considered the most powerful endogenous immune response suppressor, by inhibiting the mitogenesis of T cells, production of IL-2, and expression of soluble IL-2,[30,33] and it induces the release of anti-inflammatory cytokines such as IL-10.[3] Another proinflammatory cytokine that is rapidly released by monocytes, macrophages, and dendritic cells in the innate and adaptive immune response is IL-12, a cytokine (p70) composed of 2 subunits, 40 kDa (p40) and 35 kDa (p35). An antinociceptive effect by the suppression of the inflammatory response has been attributed to the IL-12p40 subunit.[6,44,46] Once the release of cytokines is initiated, they stimulate the recruitment of immune cells at the sites of inflammation. Chemotaxis is mediated by signaling events initiated by the binding of some cytokines, such as MIP-1α, MIP-1β (the expression of which has been involved in nociceptive transmission),[36,40] and IP-10 (an important regulator of the pain mechanism in animal models),[17,53] to their receptors. Finally, VEGF is expressed in response to cytokines and growth factors during the inflammatory process and is one of the most important inducers of angiogenesis, a critical process in healing.[38]

Our results showed that even when BGA and the USG SDIB had effects on the immune response characterized by increases in the ESR, CRP level, and WBC count during the postoperative period, the changes were greater in the BGA group. In the BGA group, immunosuppression characterized by low levels of TNF-α, IP-10, MIP-1β, and VEGF was observed, although only IL-12p40 and sIL-2RA showed significant differences between the study groups.

As all the patients underwent arthroscopic shoulder surgery, our results suggest that the changes observed in the concentrations of the evaluated inflammatory markers may be directly related to the anesthetic technique used. Events that induce hyperalgesia attract immune cells, which release proinflammatory cytokines, which in turn stimulates the nerve terminals and activates the dorsal horns of the spinal cord and the encephalon,[37,47] and regional anesthesia techniques could modify the response to stress through the regulation or inhibition of nociceptive afferent signals in the area of surgical trauma.[11,20,27,37] Specifically in patients with shoulder surgery, it has been shown that a USG SDIB or continuous infusion can reduce opioid consumption and the intensity of postoperative pain, as well as improve patient satisfaction.[1,2,9,10,14,16,22,34] Liu et al[27] showed less pain intensity on the day of surgery and a reduction in insulin levels (a stress marker) at 42 hours postoperatively in patients who underwent arthroscopic rotator cuff repair under a USG SDIB compared with BGA. Our findings were similar to those reported in the literature,[1,2,9,10,14,16,22,25,27,34] with a reduction in pain intensity in the immediate postoperative period in the USG SDIB group. No differences were observed in pain intensity evaluated at 12 hours and 24 hours after surgery, so we assume that both the BAG and the USG SDIB provided adequate analgesia for all patients.

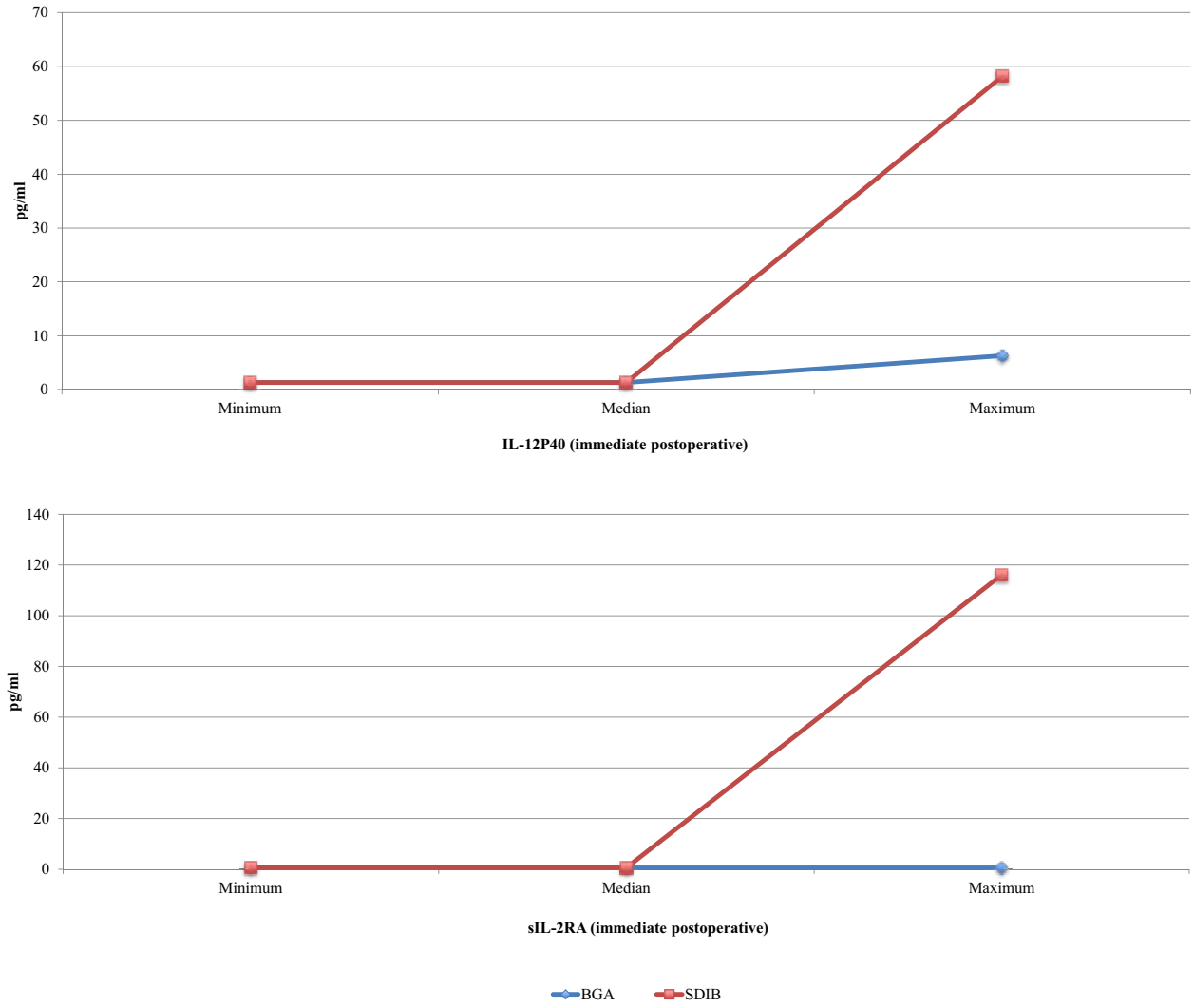

Figure 4 Minimum, median, and maximum levels of soluble interleukin 2 receptor α (*sIL-2RA*) and interleukin 12p40 (*IL-12P40*) immediately postoperatively for 2 types of anesthesia: balanced general anesthesia (*BGA*) vs. ultrasound-guided single-dose interscalene block (*SDIB*). Statistically significant differences were found when comparing the two techniques ($P < .05$).

Our study, in conjunction with other reports on the inflammatory response associated with the use of various anesthetic techniques, shows that regional anesthesia, in particular the use of nerve blocks with local anesthetics, may limit the development of local and systemic inflammation in arthroscopic shoulder surgery,[29] in addition to providing postoperative analgesia. These findings have potential clinical implications for reducing the frequency and intensity of postoperative pain, providing a shorter functional recovery time with less pain, less need for opioid analgesics, fewer associated adverse effects, and even a lower risk of infection, although the latter is rare in arthroscopic surgery.

Study limitations

We acknowledge the following limitations: (1) The small sample size may not provide sufficient power with respect to changes in cytokine and chemokine concentrations. (2) This study was an exploratory study in which multiple comparisons were made. By adjusting the P value by Bonferroni correction, some of the variables that showed significant differences between the 2 anesthesia methods (with $P < .05$) were not statistically significant with an adjusted $P < .0004$. Therefore, the results obtained for some biomarkers in this study should be confirmed in a greater number of patients. (3) A blind study was not possible as only 1 group received the USG SDIB; however, a person not involved in the surgical or anesthetic process performed the pain and cytokine concentration evaluations.

Conclusion

In arthroscopic shoulder surgery, the use of a USG SDIB compared with the use of BGA is associated with better

pain control in the immediate postoperative period and lower immunosuppression, even at 24 hours after surgery. However, it is necessary to carry out more studies that allow the confirmation of our findings, as well as to evaluate the concentration of various markers of inflammation and their association with postoperative complications, when using a USG SDIB compared with other techniques of regional or general anesthesia. Given that anesthetic drugs can have an impact on the inflammatory response, it is also important to determine whether there are differences in the concentrations of markers of inflammation depending on the type and concentration of drugs used during regional anesthesia techniques (including the USG SDIB) in shoulder arthroscopic surgery, which could modify postoperative morbidity.

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