Optimizing peripheral nerve blocks: How close can we get? Luc Sermeus 2017

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Optimizing peripheral nerve blocks: *How close can we get?*

Neuro-anatomical studies in advanced techniques of ultrasound-guided peripheral nerve blocks for increasing quality, efficacy and safety through objective evaluation

Thesis submitted in partial fulfillment of the requirements for the degree of Doctor in Medical Sciences

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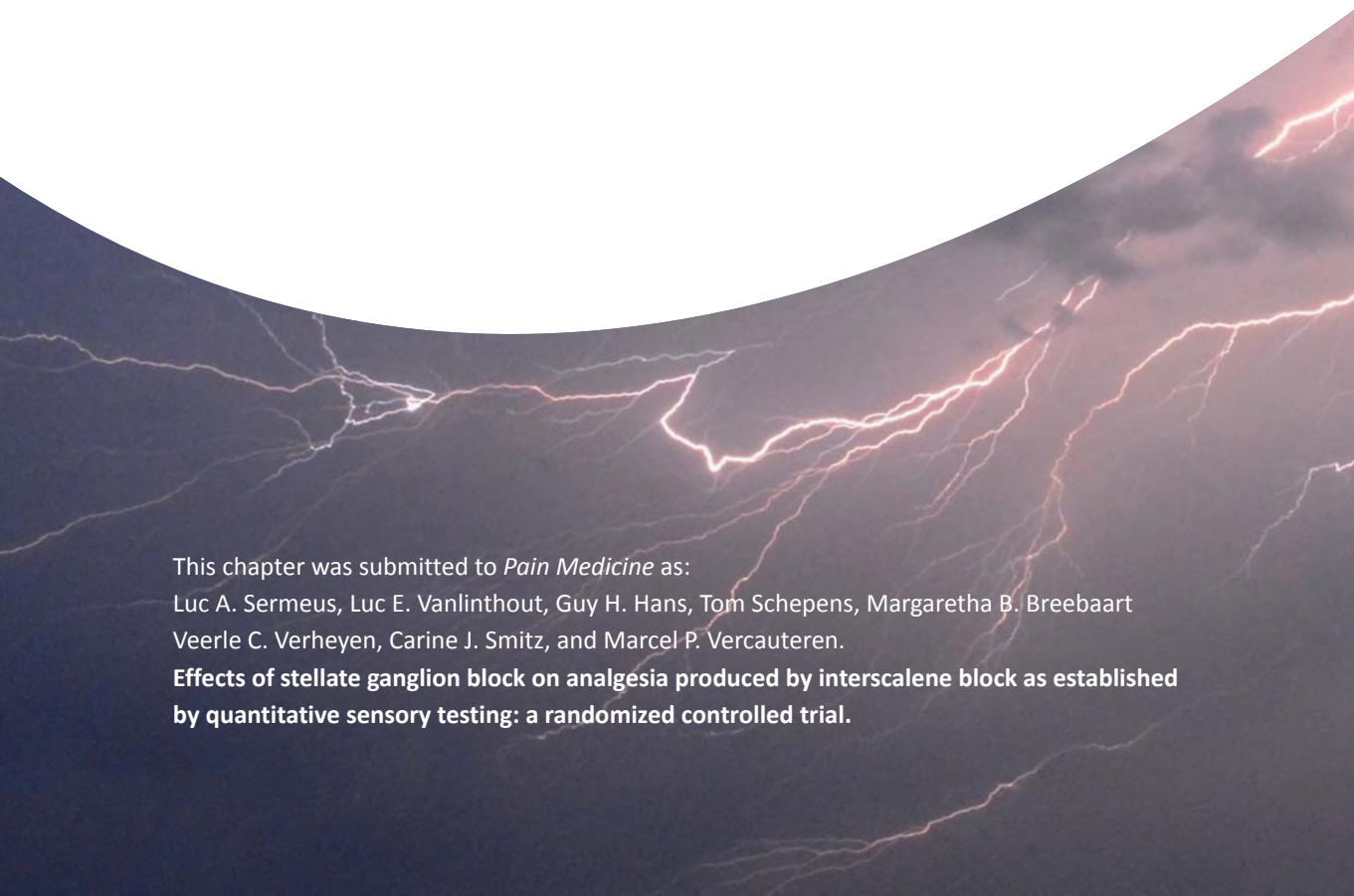
Chapter 6

Effects of stellate ganglion block on analgesia produced by interscalene block as established by quantitative sensory testing: *A randomized controlled trial*



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Effects of stellate ganglion block on analgesia produced by interscalene block as established by quantitative sensory testing: a randomized controlled trial.

Chapter 6: Contents

Abstract

Objective: To assess, by means of quantitative sensory testing, whether a stellate ganglion block could modulate the analgesia induced by inter-scalene block and/or facilitate acute nociceptive transmission.

Design: A prospective double-blind, randomized-controlled trial.

Setting: Department of anesthesia, Antwerp University Hospital, from October 2011 to December 2015.

Subjects: Twenty-eight adult patients scheduled for arthroscopy of a non-fractured shoulder, were enrolled.

Methods: Eligible participants were randomly assigned to receive either single inter-scalene block (5mL of 0.5% levobupivacaine), or combined inter-scalene and stellate ganglion block, (5mL and 3mL of 0.5% levobupivacaine respectively). Detection thresholds for cold/warm sensations and cold/heat pain were established using thermal quantitative sensory testing on C4-C7 dermatomes before local anaesthetic infiltration and at 0.5 h, 6 h, 10 h and 24 h thereafter. Our primary outcome was the time course of QST thresholds for the different neuro-sensitive/nociceptive modalities. As secondary and third outcomes, we evaluated the degree of motor block and the time to first administration of rescue analgesics.

Results: We enrolled 28 patients. No significant differences in detection thresholds for neurosensitive or nociceptive modalities, motor block or timing for rescue analgesics could be demonstrated between both groups (p=0.15-0.94).

Conclusion: Our results indicate that stellate ganglion block does not add any anti-nociceptive benefit to inter-scalene block and has no influence on this type of acute pain.

Introduction

Participation of the sympathetic nervous system in pain generation is best described in chronic, typically neuropathic pain states such as complex regional pain syndrome; however, its contribution to the generation of acute somatic pain awaits further elucidation. In contrast to animal data, surprisingly little is known about modulation of nociceptive information by the sympathetic nervous system in humans [1].

In the patient scheduled for elective surgery of the non-fractured shoulder, chronic neck and shoulder pain can induce sympathetic activation. In, for example, the arthritic shoulder joint, sensory fibers of the joint may respond to sympathetic activity [2, 3]. Furthermore, surgical insult or trauma could be the priming needed before the sympathetic nervous system can relay perioperative pain [3, 4]. Sympathetic ganglia have been the target of blockade by local anesthetics (LA) to diagnose and treat sympathetically mediated pain. It is proposed that sympathectomy interrupts the pain cycle, facilitates rehabilitation of the painful area and helps restore balanced somatic sensation [5].

The stellate ganglion, which provides sympathetic supply to the upper limb, can be selectively blocked. Such stellate ganglion blocks (SGB) confer valuable diagnostic and therapeutic benefit to sympathetically maintained pain syndromes occurring in this region [6].

However, the role of a SGB for the treatment or prevention of acute pain following upper limb surgery or trauma remains controversial. McDonnell et al. performed SGB before the surgical repair of severe upper limb trauma and achieved considerable reduction of postoperative opioid requirements [3]. Kumar et al. demonstrated the efficacy of pre-operative SGB for pain relief after surgical repair of upper limb fracture [7]. In contrast, Choi et al. were unable to find any benefit of SGB in terms of Visual Analogue Score (VAS), vital signs, and analgesic requirements during the 48 h after arthroscopic shoulder surgery [5].

To clarify inconsistencies in the available evidence, further studies should focus on the role of the sympathetic nervous system in the generation of acute postoperative pain [2]. We therefore evaluated the efficacy of

SGB to modulate analgesic effects induced by interscalene block (ISB) in a double-blind randomized controlled trial (RCT). The novelty of this study was the use of QST to monitor magnitude and time course of a combined somatic-sympathetic block. For this purpose, detection thresholds for various neuro-sensitive and nociceptive modalities were compared in carefully selected young adults who were randomly assigned to receive regional anesthesia (RA) with either single ISB or combined ISB/SGB to undergo arthroscopic surgery on the non-fractured shoulder. Sensory and nociceptive thresholds were assessed non-invasively using thermal quantitative sensory testing (QST) on dermatomes that were innervated by the C4-C7 roots of the brachial plexus.

Methodology

In this single-center prospective double-blind RCT, patients scheduled to undergo a shoulder arthroscopy were considered to receive either single ISB or combined ISB/SGB. Patients with contraindications for RA, i.e., those receiving chronic analgesic therapy for more than 3 weeks, suffering from diabetes mellitus, peripheral neuropathy and/or coagulation problems were excluded. Patients enrolled were given premedication with lorazepam 1 mg p.o. and discontinued pre-operative analgesics 12 h before surgery.

The study was performed at the Antwerp University Hospital from October 2011 to December 2015. After approval by the Institutional Ethical Committee (11/20/162), the research project was conducted in accordance with the recommendations of good clinical practice. Written informed consent was obtained from all participants.

Sealed envelopes, with random allocation cards using computer-generated random numbers, were used to randomly allocate participants to receive either a single ISB or a combined ISB/SGB (Figure 1). These envelopes were prepared by an independent researcher, who was not involved in the study. The sealed envelope was given to an unblinded anesthetist, who performed the block. Both the nurse performing the QST recordings and the anesthetist in charge of the general anesthesia were unaware of the regional technique used.

The interscalene approach was ultrasound-guided and targeted at the level of the emerging fifth cervical nerve root. Under sterile conditions, a linear 18-MHz ultrasound (US) transducer (Focus 800, BK Ultrasound, Herlev, Denmark) and a 22-gauge needle (Sonoplex 50 mm, Pajunk, Geisingen, Germany) were used. The C5 root was localized by recognizing the transverse processes of C7, C6 and C5. The needle was positioned lateral to and below the C5 root, and 5 mL of levobupivacaine 0.5% (LBup 0.5%) (Chirocaine, Abbvie SA, Wavre, Belgium) were slowly injected. To avoid subepineural injection, which could damage the root and/or influence our results, we performed a peri-plexus and tangential approach to the roots [8-10].

The injection site of the SGB was localized using the linear US transducer, and a lateral approach was performed. The transducer was placed transverse at the anterior scalene muscle, with the carotid artery medially and the brachial plexus laterally, a few millimeters caudal to the prominent anterior tubercle of C6 (Chassaignac's tubercle). The needle was inserted in plane, lateral and, posterior of the carotid artery and directed to the longus colli muscle[11]. The needle tip was positioned in the plane formed by the prevertebral fascia and the longus colli muscle. Slowly, 3 mL of LBup 0.5% were injected.

General anesthesia was induced, after the second QST assessment, with fentanyl 3 µg/kg, propofol 2 to 3 mg/kg and rocuronium 0.5 mg/kg and maintained using sevoflurane. Non-invasive blood pressure (NIBP), electrocardiography (ECG), SpO_2 and capnography were monitored either continuously (ECG, SpO_2 and capnography) or at regular intervals (NIBP). Increments of opioid were administered when the pre-induction blood pressure increased by >25%.

Thermal QST (TSA-II – NeuroSensory Analyser, Medoc Ltd., Ramat Yishai, Israel) was performed within dermatomes C4 through C7. The thermal analyser thermode was placed on the dermatomes to be tested; it induces a serial change in temperature starting at a baseline of 32°C. Surface temperature of the thermode changes at a rate of 1°C/s for non-noxious sensations and 1.5°C/s for painful stimulations. Patients set threshold values by pressing a button when they detect a change in temperature or pain. Detection thresholds for non-noxious cold and warm sensations (repre-

senting A-δ fibers and C-fibers, respectively) were recorded first. Detection thresholds for cold and heat pain (both representing A-δ and C-fibers) were subsequently documented. To avoid skin injury, increases and decreases in temperature were stopped at 50.5°C for heat pain and 0°C for cold pain.

The software of the QST analyser (Win TSA 5.32, Medoc Ltd., Ramat Yishai, Israel) uses gender, age and dermatome to identify corresponding normative values for the different thermal thresholds [12]. A blinded nurse entered these data into the QST device before establishing the baseline control value.

Thermal QST was performed 1 h before US-guided ISB (baseline control value) and at 0.5 h, 6 h, 10 h, and at 21 to 24 h after LA infiltration. QST was established in fully cooperative patients either before (baseline and at 0.5 h following LA injection) or after full recovery (at 6, 10 and at 21-24 h after LA injection) from general anesthesia. Patients with baseline QST control values that indicated the presence of hyper- or hypo-sensory phenomena were excluded.

In each dermatome (C4, C5, C6 and C7) and at each of the assessment times, five serial measurements were obtained for cold/warm sensation (CS/WS) and three serial measurements for cold/heat pain (CP/HP). The average of the serially measured detection thresholds was considered. To obtain a within-subject control value, detection thresholds for were also tested in the contralateral (unblocked) C5 dermatome.

WS/CS and HP/CP detection thresholds were established by applying the reaction-time-inclusive method of limits. Individual baseline values were used as substitute reference ranges for the normative data available for these tests. The effect of applying RA was assessed by evaluating the differences in detection thresholds for these non-noxious thermal stimuli. The degree of hypoesthesia was expressed as an absolute value of temperature change of the detection threshold between the baseline (32°C) and maximal level (50.5°C for WS and 0°C for CS) [12].

Following each QST test, the degree of motor block was evaluated using a validated 3-point modified Bromage scale [13]. Patient demographics, quantifiable characteristics and pre-operative medications were also noted.

In addition, both the need for and timing of rescue analgesic medication

were noted in the medical records. The rescue medication consisted of 1 g of paracetamol and 30 mg of ketorolac administered i.v.

Assumption 1. Assuming a difference in magnitude and duration of the regional block using a single and ISB combined with SGB to be 50% and equal variability in both groups (expected standard deviation of 37.5% in both groups), we needed 10 patients in each group (α=0.05 and β=0.8).

Our primary outcome was the time course of QST thresholds for the different neuro-sensitive/nociceptive modalities at dermatomes C4-C7. As a secondary outcome we evaluated the degree of motorblock. As a third outcome, we considered the time to rescue analgesics.

Repeated measures analysis of variance (ANOVA) was performed to compare the mean differences in outcomes for QST over different time points (baseline and after 0.5, 6, 10 and 24 h post-treatment) or dermatomes (C4, C5, C6 and C7) between groups that were defined by the blocks to which they were assigned. In addition, outcome data were modeled using the generalized estimating equation (GEE) approach. The advantage of GEE consists of a greater flexibility for handling different types of outcomes (e.g., continuous QST and non-continuous motor block tests (MBT)) and modeling a wide variety of correlation patterns between the repeated measures [14].

The times to first request for rescue analgesic and the VAS scores at these occasions were compared between the single ISB and the combined ISB/GSB groups using the non-parametric Mann-Whitney U-test (MWU). Our null hypothesis assumed no significant difference between the single ISB and the combined ISB/SGB groups for the times to rescue analgesic requirement and the VAS scores at these moments.

A value of $p<0.05$ was considered significant. Data analysis was performed using Stata (version 14, StatCorp®, College Drive, Texas, USA).

Results

Twenty-eight eligible patients were included in the study. The subjects were randomly assigned to two study groups to undergo either ISB or ISB/SGB. After an interim evaluation, we ultimately analyzed the results of 20 patients, with a sample size of 10 for each group (Figure 6.1). Patient demographics and quantifiable characteristics were similar across the two groups (Table 6.1).

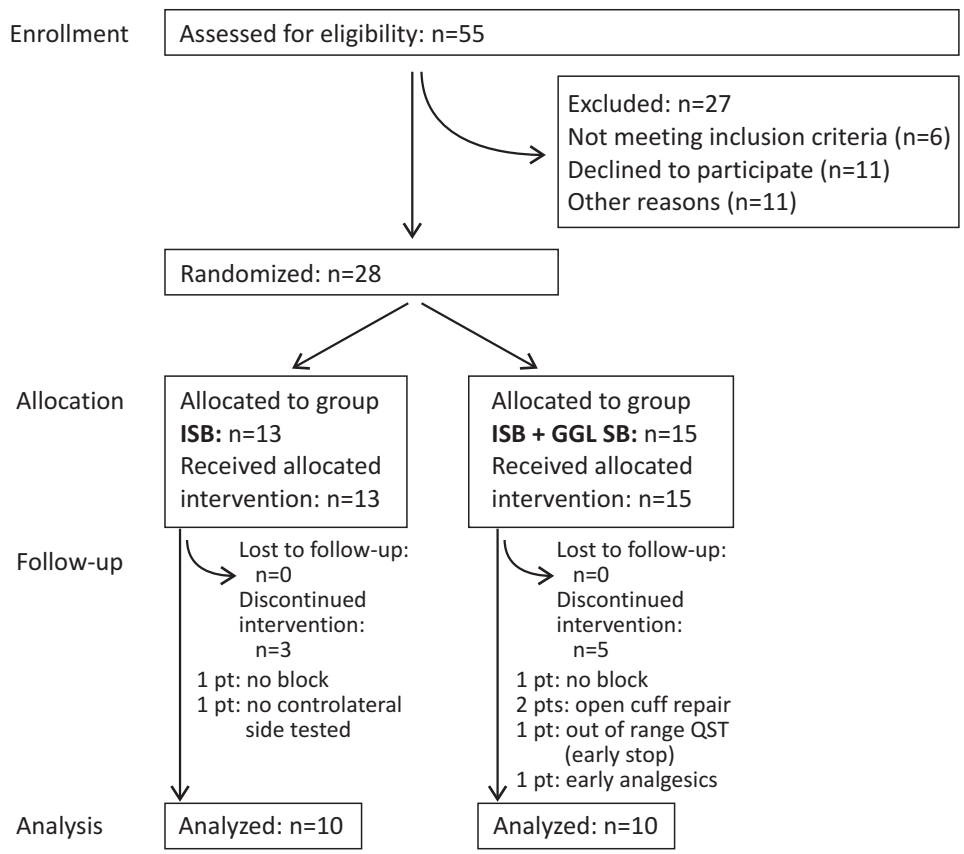

Figure 6.1. Consort 2010 flow diagram.

The QST results prior to injection were within the age-, sex- and dermatome-specific normative ranges for all 20 patients [12].

With reference to within dermatome differences in detection thresholds for the different neurosensitive (WS and CS) and nociceptive (HP and CP) modalities, the following conclusions could be made.

Table 6.1. Demographic data and quantifiable patient characteristics. Values indicate the median (IQR) [range] or number.

Patient Characteristics	**ISB**	**ISB+SGB**
N	10	10
M/F ratio	6/4	6/4
Age (y)	51 (34-55) [31 - 68]	54 (47-57) [26 - 64]
Height (cm)	172 (166-176) [164-178]	173 (154-178) [152-183]
Weight (kg)	78.0 (71.0-84.0) [63.5-98.0]	79.0 (65.0-84.7) [47.0-102.0]
BMI (kg/m²)	27.0 (23.4-29.7) [22.8-31.6]	25.8 (22.0-27.5) [21.6-33.7]

In both the ISB and ISB/SGB treatment groups, the detection thresholds for WS, CS, HP and CP at dermatome C5 and for WS and CP at dermatome C6 after 0.5, 6 and 10 h following treatment were found to be significantly different ($p<0.01$-0.001) from the corresponding values before and at 21-24 h following LA injection. At the C4 level, the thresholds for WS at 6 h (ISB and ISB/SGB) and at 10 h (ISB) and those for HP at 10 h (ISB and ISB/SGB) were found to be significantly higher. At the C6 level, the thresholds for CS at 6 h (ISB and ISB/SGB) and those for CP at 0.5 and 6 h (ISB) were found to be significantly higher after peri-plexus administration of LBup0.5%. In the C7 dermatome, thresholds for neurosensitive modalities did not change significantly for any of the time intervals assessed ($p=0.844$). In the C4-C7 dermatomes, the baseline (pretreatment) threshold values for the investigated neurosensitive modalities were not significantly different from those measured at 24 h following LA injection.

Regarding between-dermatome differences in detection thresholds for the neurosensitive (WS and CS) and nociceptive (HP and CP) modalities, the following conclusions could be made. At 0.5, 6 and 10 h following LA injection, thresholds for WS, CS, HP and CP at the C5 level were significantly

different from the corresponding values measured at the other levels (C4, C6 and C7).

Thresholds for WS, CS, HP and CP for both ISB and ISB/SGB at C4, C5, C6 and C7 are represented in Tables 6.2-6.5. The time course of WS and CS thresholds for ISB and ISB/SGB for C5 and C6 are shown in Figures 6.2 and 6.3, respectively. Between-dermatome differences for WS and CS at 0.5h following LA injection are shown in Figure 6.4.

At 30 min, motor block was complete (Grade 2) in 9/10 patients in the ISB group and in 5/10 patients in the ISB/SGB group. A decreased (Grade 1) motor response was observed in 1/10 and 5/10 participants in the ISB and ISB/SGB groups, respectively. Thus, it cannot be excluded that impaired mobility of the shoulder due to the pathology or the surgical procedure may have interfered with the rating of the motor block.

Finally, differences in corresponding values among the treatment groups for neurosensitive modalities (WS, CS, HP and CP) and for motor block according to the 3-point modified Bromage scale were not great enough to exclude the possibility that differences were simply due to sampling variability (p=0.15-0.94) (Tables 6.2-6.5 and Figures 6.2, 6.3, 6.4, and 6.5).

The times to the first request for rescue analgesic were 9.3 (9.1-9.4) [9.0-10.0] h and 9.3 (9.0-9.4) [8.7-9.8] h, and the VAS scores for these time intervals were 6.0 (5.0-6.0) [4.0-7.0] and 6 (5.3-7.8) [4.0-10] for the single ISB and combined ISB/SGB groups, respectively. Values are median (IQR) [range]. Neither for the times to first request for rescue analgesic (p=0.51), nor for the VAS scores at these occasions significant differences could be demonstrated (i.e., p=0.51 and 0.33 for the timing and the VAS scores, respectively). The null hypothesis assuming no differences between the timing and VAS scores of single ISB and combined ISB/SGB can therefore not be rejected.

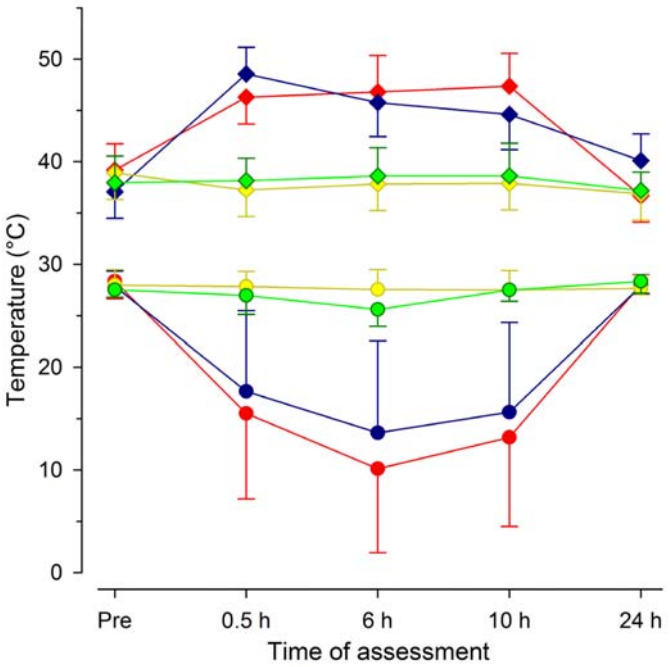

Figure 6.2. Magnitude and time course of the detection thresholds for warmth (◆) and cold (●) sensation, after both single interscalene or combined interscalene-stellate ganglion block at the ipsilateral (symbols and lines in blue or red, respectively) and contralateral (symbols and lines in green or yellow, respectively) C5 dermatomes. Values indicate the mean (◆ and ●) with error bars representing the 95% confidence intervals.

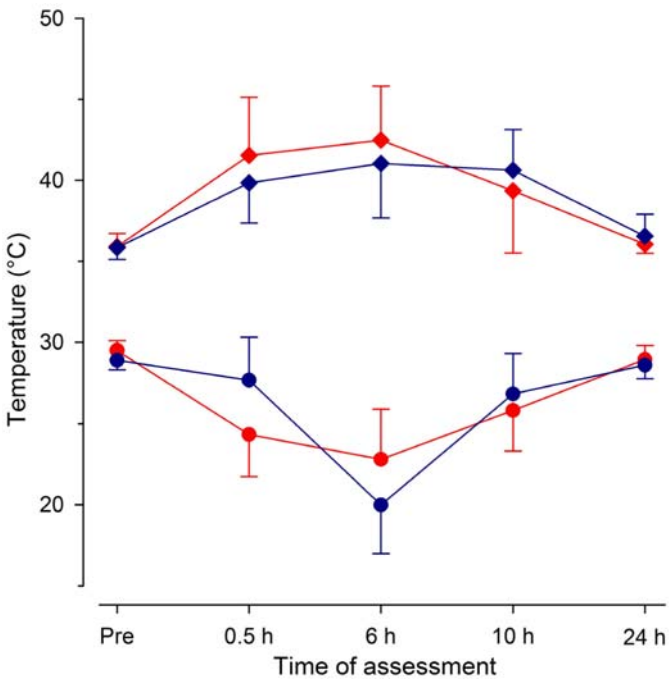

Figure 6.3. Magnitude and time course of the detection thresholds for warmth (◆) and cold (●) sensation, after both single interscalene or combined interscalene-stellate ganglion block at the ipsilateral (symbols and lines are in in blue or red, respectively) C6 dermatome. Values indicate the mean (◆ and ●) with error bars representing the 95% confidence intervals.

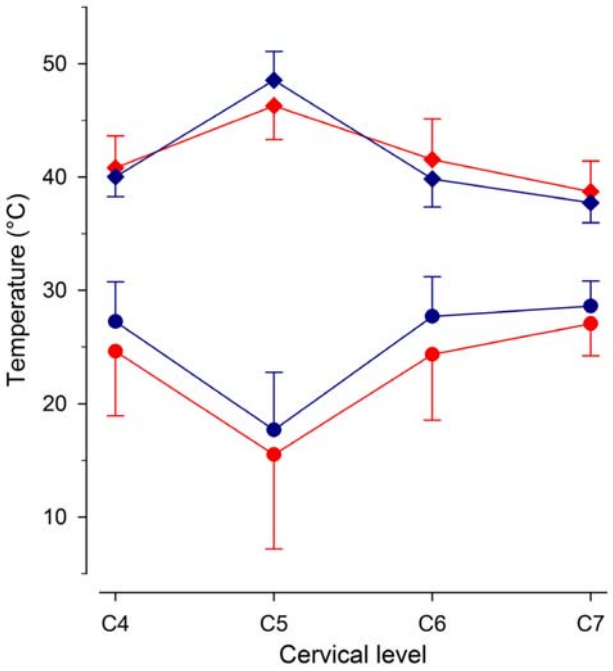

Figure 6.4. Between-dermatome differences in the magnitude of detection thresholds for warmth (◆) and cold (●) sensation, after interscalene block using low-volume, high-concentration and long-acting local anesthetic, targeted at the C5 level. This interscalene block was administered alone or combined with ipsilateral stellate ganglion block (symbols and lines are in blue or red, respectively). Values indicate the mean (◆ and ●) with error bars representing the 95% confidence intervals.

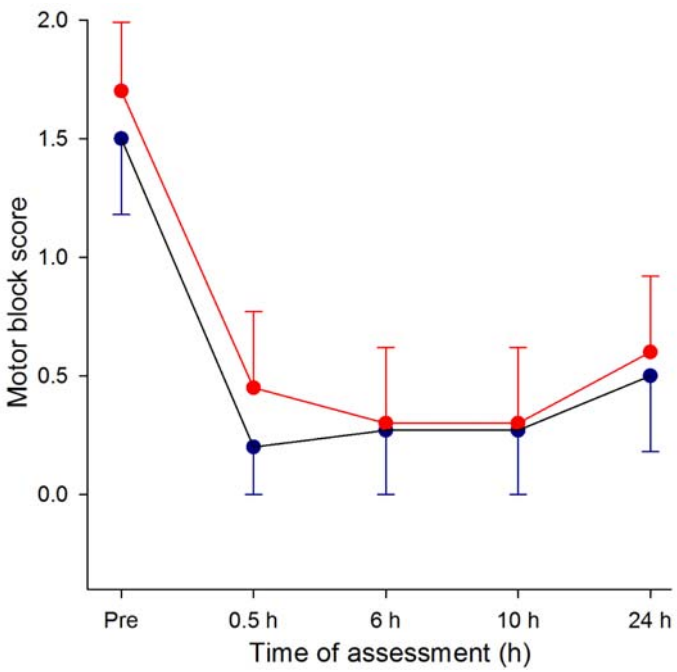

Figure 6.5. Time course of motor block after both single interscalene or combined interscalene-stellate ganglion block at the ipsilateral site (symbols and lines are in blue or red, respectively) as evaluated using the 3-point modified Bromage scale[13]. Values indicate the mean (●) with error bars representing the 95% confidence intervals.

Discussion

Although the role of the autonomic nervous system in the pathogenesis of chronic pain is clearly defined, its potential to facilitate acute nociceptive transmission has been scarcely documented. To investigate any such sympathetic nervous system involvement in the modulation of acute somatic pain, we evaluated whether SGB could contribute to the anti-nociceptive effect of RA by ISB for elective surgery on the non-fractured shoulder. By using a small volume, we could assume no cervical ganglia would be blocked in the single ISB group [15]. The assumed benefits of this combined approach refer to an earlier onset, prolonged duration, increased magnitude and greater extent of nerve block that is measured using QST. Since sensory fibers responsible for the transmission of nociception and temperature sensation (A-δ and C-fibers), are similarly affected by Levobupivacaine, changes in temperature sensation indicate the area were regional block is working[16, 17]. The novelty of this study was that we used QST to monitor magnitude and time course of regional block.

From the detection thresholds for the tested neuro-sensitive modalities in both the ISB and the ISB/SGB treatment groups, we could confirm a stable sensitive and nociceptive block at the C5 level with maximal effect between 0.5 and 10 h following the injection of LA. Furthermore, with the low-volume, high-anesthetic concentration technique used in the current study, the block at the C5 level started earlier and was more profound compared to that obtained in neighboring (C4 and C6) dermatomes. These observations suggest a reduced/delayed effect due to the ongoing spread of LA solution from the C5 level. With this approach and this volume of LA, C7 nerve roots may not be blocked. Finally, it appears that SGB does not confer added anti-nociceptive benefit to an ISB for shoulder surgery.

SGB constitutes a valuable diagnostic and therapeutic tool to sympathetically maintain pain syndromes in the head, neck, and upper extremity. Performed in advance to non-fractured surgery, it appears that SGB does not confer added anti-nociceptive benefit to an ISB. This study therefore indicates that sympathetic modulation may not be clinically important in the pain generated by minor surgery. In these cases, the level of nociceptive stimulation was presumably insufficient to evoke a sympathetic response.

When performed after a trauma, however, SGB has been demonstrated to provide pain relief. Trauma seems to be the priming needed before the sympathetic pathway can relay postoperative pain [3, 4]. Recent studies have shown that mineralized bone, marrow and periosteum are all innervated by primary afferent sensory neurons and postganglionic sympathetic neurons. The synovium is densely innervated by postganglionic sympathetic fibers that control blood flow, vascular permeability and numerous immune processes within the joint [18, 19]. Using several histochemical and imaging techniques, it was shown that the sensory fibers innervating the periosteum are organized in a unique net-like meshwork, which suggests that these sensory fibers (A-δ and peptide-rich C-fibers) may be distinctively organized to detect mechanical distortion of the periosteum and underlying mineralized bone [20-22]. Following a fracture, movement of the bone can be remarkably painful. The initial pain likely arises primarily from mechanical distortion and activation of the normally silent mechano-sensitive sensory nerve fibers in the periosteum. Following the initial sharp, arresting pain, a hematoma is formed around the fracture site, and inflammatory cells release immune mediators such as prostaglandins, bradykinins, histamine, and nerve growth factor that sensitize nerve fibers present in and around the fracture site [23, 24]. Following injury to the young healthy bone, there is a small sprouting of sensory and sympathetic fibres around the site of bone fracture [25, 26].

The net effect of stress on pain sensation reflects a balance between descending spinal inhibition and sympathetic outflow that can shift towards pain facilitation when central and peripheral α-2-adrenoceptor inhibitory mechanisms are attenuated [27]. When sympathetic nervous system outflow is disinhibited (less inhibited, hence activated), and inhibition by descending pain inhibitory projections is reduced, the effect of sympathetic nervous system on primary afferents can be amplified, unmasking stress-induced hyperalgesia. Physiologically, disinhibition of sympathetic nervous system outflow and reduced descending inhibition could result from α-2 receptor desensitization due to sustained norepinephrine outflow induced by intense and protracted stress [28]. When sympathetic nervous system outflow is increased and descending inhibition is diminished, the effects of stress, sensitizing and nociceptive stimuli could be expected to result

in a positive feedback loop that triggers enhanced sensation of pain [28, 29].

The use of SGB solely for the management of acute nociceptive pain has scarcely been documented. A recent meta-analysis found only a single study with level-1B evidence and a handful of series with level-1C evidence on the use of SGB [30]. Although many authors have stated the effectiveness of SGB, there is a paucity of high-quality evidence. We share the views of Chambers and Smith who discussed the series by McDonnell et al. and cautioned against using SGB for postoperative analgesia in routine practice, as the mechanism is not completely understood [31].

QST, a reliable way of assessing small sensory nerve function, has been used to compare block characteristics such as onset, intensity and duration after ISB [32]. Quantitative sensory testings (QSTs) are techniques employed to measure the intensity of stimuli needed to produce specific sensory perceptions. They are used to evaluate a sensory detection threshold or other sensory responses from supra-threshold stimulation. QST is a method frequently applied to assess small-fiber neuropathies, and these small fibers, i.e., the A-δ and C-fibers, constitute the peripheral part of the afferent pathway for pain transmission. QST can therefore assess the integrity of the entire sensory neuroaxis from peripheral nerves to the cortical structures relevant to sensory perception [33]. In the ascending spinal pathway conducting pain-related information, as in the brainstem, somato-autonomic connections are made, indicating a possible interaction by the autonomic nervous system at different levels of the afferent pathway for pain perception [34].

Some potential risks and limitations of the current study must be considered. The first is the small number of patients who were included**.** The current study compared two RA techniques for their ability to relieve the pain associated with arthroscopic surgery of the shoulder. We selected our population carefully using rigid inclusion criteria, as described in the text, to reduce patient variability. However, this approach inevitably introduced constraints such as the availability of large numbers of patients within a reasonable period of time.

Both the investigator and clinician should be concerned about the ability to detect an important clinical difference. Different investigators disagree on what is a clinically significant difference [35] as well as the risk they are

willing to take to miss a meaningful benefit of treatment. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has defined 10–20% decrease as minimally important, 30% as moderately important, and 50% as substantial [36]. Assuming a clinically meaningful difference of 50% and a standard deviation that is 75% of this value, i.e. 37.5%, 10 patients in each group were required (α=0.05 and β=0.8).

Second, the reliability of QST should be addressed. The use of QST has become more widespread, with increasing focus on describing somatosensory profiles. However, the reliability of thermal QST has yet to be established. A narrative meta-analysis of 21 studies was undertaken, and the results showed considerable variability in the reliability of each thermal QST parameter, but overall, the reliability of cold and warm detection thresholds ranged from poor to excellent, while heat and cold pain thresholds ranged from fair to excellent [37]. Besides, the assessment of detection thresholds is constrained/censored by the window/range/upper and lower limits of temperatures (0-50.5°C) that is/are allowed for QST. If the maximum stimulus is reached with the patient still indicating sensation, the maximum value is recorded as a threshold. This may have imposed an artificial floor or ceiling effect to response values (0-50.5°C), thus distorting the results.

Third, the model proposed does not preclude the possibility that epinephrine from the adrenal medulla contributes to the sensitization of nociceptors after injury. This effect may be caused by the humoral component of the sympathetic response, which is not controlled by the nerve block.

Fourth, some patients display Horner's syndrome after interscalene blockade, even after ultrasound-guided injection. In this study, with the small volume injected, we didn't observe any Horner's syndrome in the single ISB group.

In conclusion, we evaluated the efficacy of SGB to modulate the analgesic effects induced by ISB. For this purpose, detection thresholds for various neuro-sensitive and nociceptive modalities were compared in adults who were assigned to receive either ISB or ISB/SGB to undergo arthroscopic procedures. Sensory and nociceptive thresholds were assessed non-invasively using thermal QST on dermatomes of the brachial plexus. The results indicate that SGB does not confer added anti-nociceptive benefit to ISB in

non-fractured shoulder surgery. Even if an ultrasound-guided SGB is a relative easy procedure in experts' hands, these results show that it isn't worth to take the risk of an additional puncture in elective shoulder arthroscopy.

Therefore, sympathetic modulation may not be clinically important in the pain generated by minor surgery. However, we cannot exclude that epinephrine from the adrenal medulla contributes to the sensitization of nociceptors after injury, as this adrenergic agent constitutes the humoral component of the sympathetic response, which is not controlled by the nerve block.

Supplementary material

Table 6.2. Time course of mean **warmth sensitivity** detection thresholds at dermatomes C4 through C7 after performing interscalene block (ISB) alone or combined with stellate ganglion block (SGB).

Time of Assessment	Cervical 4		Cervical 5	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	37.5 [36.5-38.5]	38.0 [36.5-41.9]	37.1 [35.4-38.7]	39.2 [36.5-41.9]
0.5 h	40.0 [38.3-41.8]	40.8 [38.0-43.6]	48.6 [47.2-49.9]*,¶	46.3 [43.3-49.3]*,¶
6 h	43.0 [39.5-46.5]*	41.3 [37.9-44.7]*	45.8 [42.4-49.1]*,¶	46.8 [43.2-50.0]*,¶
10 h	41.6 [38.9-44.2]*	40.7 [38.1-43.4]	44.6 [41.2-48.0]*,¶	47.4 [44.2-50.0]*,¶
21-23 h	38.5 [37.5-39.5]	38.5 [36.5-40.5]	40.1 [36.9-43.3]	36.7 [35.6-37.8]
	Cervical 6		Cervical 7	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	35.8 [35.1-36.6]	35.9 [35.1-36.7]	36.9 [35.4-38.4]	35.7 [34.5-36.8]
0.5 h	39.8 [37.3-42.3]*	41.5 [37.9-45.1]*	37.7 [36.0-39.5]	38.7 [36.0-41.4]
6 h	41.0 [37.7-44.4]*	42.5 [39.1-45.8]*	39.0 [35.9-42.1]	38.7 [35.6-41.7]
10 h	40.6 [38.1-43.1]*	39.4 [35.5-43.2]*	36.2 [32.1-40.4]	37.9 [35.2-40.5]
21-23 h	37.2 [35.9-38.6]	36.0 [35.5-36.6]	35.8 [30.6-40.9]	36.8 [35.6-38.0]

Values indicate the mean [95% confidence interval].
Within-dermatome differences of mean detection thresholds for a given regional technique at different times: * significantly different from the baseline (pre-block) control values ($p<0.001$).
Between-dermatome differences of mean detection thresholds for a given regional technique and time of assessment: ¶ significantly different from the corresponding values for a given time of assessment at other levels ($p<0.001$).
The differences in corresponding mean values among the treatment groups, i.e., ISB and ISB+SGB, were not significant ($p=0.1$-0.9).

Table 6.3. Time course of mean **cold sensitivity** detection thresholds at dermatomes C4 through C7 after performing interscalene block (ISB) alone or combined with stellate ganglion block (SGB).

Time of Assessment	Cervical 4		Cervical 5	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	28.3 [27.5-29.0]	28.5 [26.8-30.3]	27.5 [26.4-28.7]	28.3 [26.6-30.0]
0.5 h	27.3 [26.7-27.8]	24.6 [18.9-30.3]	17.7 [9.9-25.5]*¶	15.5 [7.2-23.8]*¶
6 h	23.9 [18.1-29.7]	24.6 [18.8-30.4]	13.6 [4.7-22.5]*¶	10.1 [1.9-18.3]*¶
10 h	25.4 [19.8-30.9]	26.4 [23.6-29.1]	15.6 [6.9-24.3]*¶	13.2 [4.5-21.8]*¶
21-23 h	28.3 [27.7-29.0]	28.3 [27.0-29.6]	27.9 [26.8-29.0]	28.0 [27.1-29.0]
	Cervical 6		Cervical 7	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	28.9 [27.7-30.1]	29.5 [28.9-30.1]	28.3 [27.5-29.0]	28.5 [26.8-30.3]
0.5 h	27.7 [26.5-29.0]	24.3 [18.6-30.1]	27.3 [26.7-27.8]	24.6 [18.9-30.3]
6 h	20.0 [13.0-27.0]*	22.8 [15.3-30.3]*	23.9 [18.1-29.7]	24.6 [18.8-30.4]
10 h	26.8 [25.1-28.6]	25.8 [19.8-31.8]	25.4 [19.8-30.9]	26.4 [23.6-29.1]
21-23 h	28.6 [27.7-29.6]	29.0 [28.1-29.8]	28.3 [27.7-29.0]	28.3 [27.0-29.6]

Values indicate the mean [95% confidence interval].
Within-dermatome differences of mean detection thresholds for a given regional technique at different times: * significantly different from the baseline (pre-block) control values ($p<0.001$).
Between-dermatome differences of mean detection thresholds for a given regional technique and time of assessment: ¶ significantly different from corresponding values for a given time of assessment at other levels ($p<0.001$).
The differences in corresponding mean values among the treatment groups, i.e., ISB and ISB+SGB, were not significant ($p=0.3-0.9$).

Table 6.4. Time course of mean **heath pain** detection thresholds at dermatomes C4 through C7 after performing interscalene block (ISB) alone or combined with stellate ganglion block (SGB).

Time of Assessment	Cervical 4		Cervical 5	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	47.5 [45.7-49.3]	45.0 [42.0-47.9]	47.7 [46.4-49.1]	47.8 [46.2-49.5]
0.5 h	48.5 [46.8-50.2]	47.1 [44.7-49.4]	50.5 [50.4-50.5]*¶	50.1 [49.8-50.5]*¶
6 h	48.4 [46.9-49.8]	47.8 [45.7-49.9]	50.5 [50.4-50.5]*¶	50.2 [49.7-50.5]*¶
10 h	49.2 [48.3-50.2]*	48.0 [46.0-50.0]*	50.2 [49.8-50.5]*¶	49.6 [48.2-50.5]*¶
21-23 h	48.4 [47.0-49.8]	46.8 [44.8-48.8]	48.8 [47.7-49.8]	47.6 [46.0-49.2]
	Cervical 6		Cervical 7	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	45.2 [42.9-47.4]	43.5 [40.7-46.2]	48.3 [46.1-50.4]	46.2 [43.8-48.7]
0.5 h	48.7 [47.1-50.2]*	48.7 [46.8-50.5]*	48.7 [47.1-50.2]	48.7 [47.4-50.0]
6 h	49.3 [48.2-50.3]*	48.9 [47.4-50.5]*	48.2 [46.6-49.7]	47.0 [44.5-49.6]
10 h	48.9 [47.9-49.9]*	44.5 [41.9-47.1]¶§	49.2 [47.8-50.5]	46.5 [44.4-48.6]
21-23 h	47.7 [46.2-49.2]	45.8 [43.8-47.7]	48.3 [47.0-49.5]	47.2 [45.6-48.8]

Values indicate the mean [95% confidence interval].
Within-dermatome differences of mean detection thresholds for a given regional technique at different times: * significantly different from the baseline (pre-block) control values ($p<0.001$).
Between-dermatome differences of mean detection thresholds for a given regional technique and time of assessment: ¶ significantly different from the corresponding values for a given time of assessment at other levels ($p<0.001$).
§ Significantly different from the mean values among the other corresponding treatment groups ($p<0.001$).

Table 6.5. Time course of mean detection thresholds for **cold pain** at dermatomes C4 through C7 after performing interscalene block (ISB) alone or combined with stellate ganglion block (SGB).

Time of Assessment	Cervical 4		Cervical 5	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	8.0 [1.7-14.2]	7.5 [1.2-13.7]	11.2 [4.2-18.1]	6.3 [0.01-12.6]
0.5 h	1.9 [0.01-5.6]	4.5 [0.2-9.8]	0.1 [0-0.2]*,¶	0.0*,¶
6 h	2.4 [0.01-6.2]	3.8 [0.01-7.8]	0*,¶	2.1 [0.01-4.5]*,¶
10 h	2.8 [0.01-8.1]	4.3 [0.01-9.2]	0*,¶	2.3 [0.01-6.9]*,¶
21-23 h	6.8 [0.3-13.4]	3.9 [0.01-8.1]	6.3 [0.5-11.5]	7.7 [1.6-13.8]
	Cervical 6		Cervical 7	
	ISB	ISB+GSB	ISB	ISB+GSB
Baseline	10.5 [6.0-15.1]	9.2 [3.2-15.2]	5.4 [1.5-9.4]	11.6 [5.4-17.8]
0.5 h	1.7 [0.01-3.2]*	4.4 [0.01-9.0]	5.4 [0.7-10.0]	6.9 [1.9-11.9]
6 h	1.0 [0.02-2.1]*,¶	4.9 [0.01-10.2]	6.1 [1.5-10.7]	5.2 [0.2-10.3]
10 h	5.8 [1.6-9.9]	6.3 [1.3-11.2]	6.0 [1.4-10.6]	6.1 [1.1-11.0]
21-23 h	4.8 [1.7-7.8]	8.8 [4.6-13.1]	6.5 [1.7-11.4]	9.3 [5.0-13.6]

Values indicate the mean [95% confidence interval].
Within-dermatome differences of mean detection thresholds for a given regional technique at different times: * significantly different from the baseline (pre-block) control values ($p<0.007$-0.005).
Between-dermatome differences of mean detection thresholds for a given regional technique and time of assessment: ¶ significantly different from the corresponding values for a given time of assessment at other levels ($p<0.005$-0.05).
The differences in corresponding mean values among the treatment groups, i.e., ISB and ISB+SGB, were not significant ($p=0.08$-0.9).

References

1. Karnwal A, Liao W, Julka IS, Kakazu CZ. Stellate ganglion block for postoperative analgesia in patients with upper extremity orthopaedic injuries. *Anaesthesia* 2011; 66: 1052-3
2. Kidd BL, Cruwys S, Mapp PI, Blake DR. Role of the sympathetic nervous system in chronic joint pain and inflammation. *Annals of the Rheumatic Diseases* 1992; 51: 1188-91
3. McDonnell JG, Finnerty O, Laffey JG. Stellate ganglion blockade for analgesia following upper limb surgery. *Anaesthesia* 2011; 66: 611-4

4 Bantel C, Trapp S. The role of the autonomic nervous system in acute surgical pain processing - what do we know? *Anaesthesia* 2011; 66: 541-4

5. Choi EM, Kim EM, Chung MH, et al. Effects of ultrasound-guided stellate ganglion block on acute pain after arthroscopic shoulder surgery. *Pain Physician* 2015; 18: E379-88
6. Rho RH, Brewer RP, Lamer TJ, Wilson PR. Complex regional pain syndrome. *Mayo Clinic Proceedings* 2002; 77: 174-80
7. Kumar N, Thapa D, Gombar S, Ahuja V, Gupta R. Analgesic efficacy of pre-operative stellate ganglion block on postoperative pain relief: a randomised controlled trial. *Anaesthesia* 2014; 69: 954-660
8. Spence BC, Beach ML, Gallagher JD, Sites BD. Ultrasound-guided interscalene blocks: understanding where to inject the local anaesthetic. *Anaesthesia* 2011; 66: 509-14
9. Szerb JJ, Greenberg JL, Kwofie MK, et al. Histological confirmation of needle tip position during ultrasound-guided interscalene block: a randomized comparison between the intraplexus and the periplexus approach. *Canadian Journal of Anaesthesia* 2015; 62: 1295-302
10. Sermeus LA, Sala-Blanch X, McDonnell JG, et al. Ultrasound-guided approach to nerves (direct vs. tangential) and the incidence of intraneural injection: a cadaveric study. *Anaesthesia* 2016; in press: Accepted 24 November 2016
11. Bhatia A, Flamer D, Peng PW. Evaluation of sonoanatomy relevant to performing stellate ganglion blocks using anterior and lateral simulated approaches: an observational study. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2012; 59: 1040-7
12. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006; 123: 231-43
13. Bromage PR. Mechanism of Action. Philadelphia, PA: WB Saunders, 1978; 119-59
14. Ma Y, Mazumdar M, Memtsoudis SG. Beyond repeated-measures analysis of variance: advanced statistical methods for the analysis of longitudinal data in anesthesia research. *Regional Anesthesia and Pain Medicine* 2012; 37: 99-105
15. Riazi S, Carmichael N, Awad I, Holtby RM, McCartney CJ. Effect of local anaesthetic volume (20 vs 5 ml) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. *British journal of anaesthesia* 2008; 101: 549-56
16. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001; 413: 203-10

17. Rosenberg PH, Heinonen E. Differential sensitivity of A and C nerve fibres to long-a cting amide local anaesthetics. *British journal of anaesthesia* 1983; 55: 163-7

18. Janig W. Sympathetic nervous system and inflammation: a conceptual view. *Autonomic Neuroscience* 2014; 182: 4-14

19. Schaible HG, Straub RH. Function of the sympathetic supply in acute and chronic experimental joint inflammation. *Autonomic Neuroscience* 2014; 182: 55-64

20. Mach DB, Rogers SD, Sabino MC, et al. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience* 2002; 113: 155-66

21. Martin CD, Jimenez-Andrade JM, Ghilardi JR, Mantyh PW. Organization of a unique net-like meshwork of CGRP+ sensory fibers in the mouse periosteum: implications for the generation and maintenance of bone fracture pain. *Neuroscience Letters* 2007; 427: 148-52

22. Jimenez-Andrade JM, Mantyh WG, Bloom AP, et al. A phenotypically restricted set of primary afferent nerve fibers innervate the bone versus skin: therapeutic opportunity for treating skeletal pain. *Bone* 2010; 46: 306-13

23. Petho G, Reeh PW. Sensory and signaling mechanisms of bradykinin, eicosanoids, platelet-activating factor, and nitric oxide in peripheral nociceptors. *Physiological Reviews* 2012; 92: 1699-775

24. Hukkanen M, Konttinen YT, Santavirta S, et al. Rapid proliferation of calcitonin gene-related peptide-immunoreactive nerves during healing of rat tibial fracture suggests neural involvement in bone growth and remodelling. *Neuroscience* 1993; 54: 969-79

25. Yasui M, Shiraishi Y, Ozaki N, et al. Nerve growth factor and associated nerve sprouting contribute to local mechanical hyperalgesia in a rat model of bone injury. *European Journal of Pain* 2012; 16: 953-65

26. Chartier SR, Thompson ML, Longo G, Fealk MN, Majuta LA, Mantyh PW. Exuberant sprouting of sensory and sympathetic nerve fibers in nonhealed bone fractures and the generation and maintenance of chronic skeletal pain. *Pain* 2014; 155: 2323-36

27. Khasar SG, Miao FJ, Janig W, Levine JD. Vagotomy-induced enhancement of mechanical hyperalgesia in the rat is sympathoadrenal-mediated. *The Journal of Neuroscience* 1998; 18: 3043-9

28 Quartilho A, Mata HP, Ibrahim MM, et al. Production of paradoxical sensory hypersensitivity by alpha 2-adrenoreceptor agonists. *Anesthesiology* 2004; 100: 1538-44

29. Donello JE, Guan Y, Tian M, et al. A peripheral adrenoceptor-mediated sympathetic mechanism can transform stress-induced analgesia into hyperalgesia. *Anesthesiology* 2011; 114: 1403-16

30. Day M. Sympathetic blocks: the evidence. *Pain Practice* 2008; 8: 98-109

31. Chambers WA, Smith WC. Case reports of novel treatments - proper evaluation before clinical use. *Anaesthesia* 2011; 66: 539-40

32. Sermeus LA, Hans GH, Schepens T, et al. Thermal quantitative sensory testing to assess the sensory effects of three local anesthetic solutions in a randomized trial of interscalene blockade for shoulder surgery. *Canadian Journal of Anaesthesia* 2016; 63: 46-55

33. Backonja MM, Walk D. QST in peripheral nerve injury pain disorders. *Pain* 2012; 153: 736-7

34. Cortelli P, Pierangeli G. Chronic pain-autonomic interactions. *Neurological Sciences* 2003; 24: S68-70

35. Freiman JA, Chalmers TC, Smith H, Jr., Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. Survey of 71 "negative" trials. *New England Journal of Medicine* 1978; 299: 690-4

36. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *The journal of pain : official journal of the American Pain Society* 2008; 9: 105-21

37. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: a systematic review. *Journal of Rehabilitation Research and Development* 2012; 49: 191-207