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ORIGINAL RESEARCH

Supraclavicular regional anaesthesia affecting bispectral index as level of consciousness monitor (SUPRABLOC): a pilot randomised controlled trial

F Scannell,[1] T Esterhuizen,[2] R Naidoo,[3] S Chetty[1]

[1] *Department of Anaesthesiology and Critical Care, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa*
[2] *Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa*
[3] *Private Practice, South Africa*
Corresponding author, email: *scannelldoc@gmail.com*

Background: Renewed interest in regional anaesthesia during the recent COVID-19 pandemic has inspired application of neuraxial anaesthesia for previously unconventional indications, such as awake abdominal surgeries. These patients needed little sedation, since studies demonstrate that neuraxial anaesthesia causes sedation as measured by the bispectral index (BIS). In contrast, no published study has investigated the possible sedative effects of non-neuraxial regional anaesthesia. This pilot randomised controlled trial (RCT) was designed as a template for, and to test the feasibility of, performing a definitive RCT to establish if non-neuraxial regional anaesthesia has any sedative effect.

Methods: Forty participants presenting for forearm surgery were randomly allocated to two treatment groups (supraclavicular block and control). Their level of sedation was monitored with BIS prior to surgery for 60 minutes. Specific feasibility outcomes were planned and data were collected according to CONSORT 2010 recommendations.

Results: Out of 48 patients screened, 41 (85.42%) were invited to participate. Forty patients (97.56%) consented and 100% of these completed the study. In four participants (10%), BIS electrodes needed replacement, while inadequate contact was shown in three participants (7.50%). Data collection and form completion were deemed "easy" and block success rate was 100%. Differences in mean BIS between groups were < 5 and a difference of 10% between groups in incidence of BIS < 80 (85% block group, 75% control group) was shown.

Conclusion: We propose that progression to formal RCT is feasible only with specific modifications to the study design. The decrease in BIS value from baseline should be measured per patient and a clinically significant decrease should be estimated; emergency patients should be excluded; the sample size should be 500 patients; and multiple trial sites should be used. Further consideration should be given to whether such a trial would provide clinically useful information, and would justify the risks, patient discomfort and the considerable financial cost.

Keywords: regional, supraclavicular, bispectral, BIS, pilot, feasibility, sedation

Introduction

Recently there has been an increased interest in regional anaesthesia, especially during the COVID-19 pandemic, due to the avoidance of aerosol-generating procedures, reduced postoperative complications and the need to decrease the length of patients' hospital stay.[1] To illustrate, case series have been published of awake abdominal surgeries safely being performed under neuraxial anaesthesia.[2,3] These patients needed either no sedation intraoperatively or only light sedation.[2,3] The reason for this is illustrated by studies that have shown a link between neuraxial anaesthesia and decreased level of consciousness (LOC) as measured by the bispectral index (BIS).[4-11] To date however, there has been little discussion about the relationship between non-neuraxial regional anaesthesia and decreased LOC.

In order to investigate whether such a relationship exists, the ideal study design would be a formal randomised controlled trial (RCT). Sample size calculations for such a trial could not be established due to a lack of data about the control population. A pilot RCT was therefore conducted to determine the feasibility of this study.

For pilot trials, specific outcomes need to be established in accordance with CONSORT 2010 guidelines[12] and known pilot RCT formats.[13,14] Assessment of the use of specific equipment, data forms and block success rate would provide valuable information that would impact feasibility. For the same reason, information regarding patient screening, recruitment and retaining should be included in feasibility studies. The outcome of such a feasibility study could be that the main study is not feasible, is feasible with modifications, is feasible without modifications with close monitoring or is feasible without modifications.[14]

In this pilot study, we compared BIS values of participants receiving supraclavicular brachial plexus blocks to participants not receiving blocks in the induction room environment in the hour preceding surgery. The trial was designed to function as a template for a definitive large-scale RCT, specifically as a randomised, single blinded, parallel two-armed trial with one-

to-one allocation. The aim of this pilot trial was to determine if a larger trial could and should be done by assessing specific feasibility objectives. We hypothesised that a formal RCT would, indeed, be feasible.

Methods

Sample size calculation

Sample size estimates for a formal RCT were attempted using data from a sleep study done by Tung et al.[15] where 17 out of 28 participants (60%) were able to fall asleep (correlating with BIS values below 80) during daylight hours in a darkened room within 30 minutes while attached to a BIS monitor. A study by Naidoo[16] showed that 65% of participants who received a supraclavicular block had BIS values below 80. This difference of 5% (between 65% and 60%) was not considered to be clinically important.

In comparison to the participants in the Tung et al.[15] study, who had optimal conditions for sleep, our study participants were preparing to undergo surgery and experiencing associated anxiety. We proposed that the incidence of BIS values below 80 in the control group would be closer to 40%. Assuming this new control proportion of 40% with a proportion of 60% in the intervention group, the sample size needed to prove a statistical difference ($p < 0.05$) with a power of 80% and confidence intervals of 95% (two sided 2.5%), indicating 60 participants in each group of a formal RCT.

The research team decided on a pilot RCT aiming to assess the feasibility of a formal RCT. Using a minimum of 10% of the sample required for a formal study (sample size of 12 participants),[17] we aimed to recruit 40 participants with a 1:1 allocation ratio.

Study design and setting

The Health Research Ethics Committee of Stellenbosch University (M19/05/014) approved this single blinded pilot RCT which was designed to assess the feasibility of performing a formalised trial looking at the possible sedating effect of supraclavicular brachial plexus blockade. Eligible patients presenting for elective and emergency orthopaedic forearm, wrist and hand surgery at Tygerberg Hospital (tertiary referral hospital) between December 2019 and July 2020 were invited to participate.

The following are the exclusion criteria:

- American Society of Anesthesiologists (ASA) class 3 or more
- Not fasted ≥ 6 hours preoperatively
- Known allergies to the local anaesthetics used
- Signs of peripheral neuropathy or other neurological disorder affecting the limb to be blocked
- Failed block or block complications
- Contraindication to peripheral nerve block (including bleeding tendencies)
- Sedation required in the induction room due to anxiousness or any other reason
- Known systemic neurological or psychiatric illnesses or receiving neuroleptic medication
- Receiving narcotics, anxiolytics or analgesics in the preceding 8 hours
- Baseline oxygen saturation on room air < 94%
- Patients < 18 or > 65 years of age
- Patients whose oxygen saturation decreased to below 94% or whose blood pressure deviated > 20% from baseline values after receiving the block
- Patients refusing to participate in the study
- Patients with a pre-block numerical visual analogue scale (VAS) pain score ≥ 4

Patients who would have been excluded after initiation of the study would have been excluded from BIS data collection and calculations, but would have been noted as part of study outcomes. This, however, was not applicable as no participants met exclusion criteria after initiation of the study.

Data collection

All patients who met inclusion criteria were screened for exclusion criteria by the principal investigator (PI) and then invited to participate in the study. Informed consent was obtained prior to recruitment into the study in accordance with Good Clinical Practice Guidelines.[18] Randomisation was done using a computer-generated random sequence (https://www.randomizer.org/) to produce a series of sealed envelopes containing 1:1 group allocation and a unique study number. Following recruitment, the participants' hospital label was placed on a participant identification form linking them to the unique study number. The corresponding envelope was opened and the allocated study group documented.

Following application of monitors, baseline measurements (blood pressure, heart rate and oxygen saturation) were recorded. Electronic recording of continuous BIS values was started and data were automatically collected from the monitor trend interface (BIS Vista module, Medtronic Africa, Pty. Ltd.) and transferred as a PDF file onto a USB flash drive (Sandisk Ultra USB 3.0 Flash Drive 32GB) after completion of the study.

All participants were placed in a supine position and blood pressure cycling was started on a 5 minute cycle to serve as a reference point for the observer to collect data (immediately for control participants and after block completion for intervention participants). For intervention participants, supraclavicular brachial plexus blocks were performed using a Sonosite M-Turbo (FUJIFILM SonoSite, Inc., Bothell, WA, 98021, USA) ultrasound machine and 13-6 MHz linear probe (HFL38X CIMT). Using an aseptic technique, a 50 mm 22 gauge short bevel insulated hyperechoic needle (Ultraplex D, insulated needle with extension set, 30° bevel STIMD2250/30) was used to perform the block with 0.5% bupivacaine (2 mg/kg of ideal body weight up to maximum 100 mg). No nerve stimulation was used.[19]

Table I: Outcomes and criteria for assessing feasibility to progress to formal RCT

	Outcomes	Criteria for progress to RCT
Primary	Proportion of eligible patients after screening	≥ 50% of patients screened
	Rate of acceptance to participate in the study	≥ 50% of patients invited
	Study completion rate	≥ 80%
	Amount of BIS electrodes needing replacing	≤ 15%
	Proportion of inadequate BIS contact	< 10% of all patients show contact drop ≥ 15%
	Opinion of the ease of completing data form	Median value > 3/5 (1 – very difficult, 2 – slightly difficult, 3 – normal difficulty, 4 – relatively easy, 5 – easy)
	Block success rate	> 90%
Secondary	Mean and standard deviation of BIS values estimated by treatment group, proportion of BIS values below 80 calculated by group	Minimum clinically important difference (MCID) between treatment groups estimated as a difference in mean BIS value of ≥ 10 and a difference of patients in whom BIS values drop below 80 ≥ 20%
	Sample size for formal RCT	Up to 300 patients in total

For both control and intervention participants, the lights in the induction room were dimmed, the participants were made comfortable and the observer (blinded to intervention) was called to begin data collection on a separate form. The observer ensured that the induction room environment remained quiet. Blood pressure, heart rate, oxygen saturation level and time were recorded every 10 minutes for the hour following the block (or lack thereof) using the first restart of blood pressure cycling after the intervention had been performed as a reference for "time 0". Participant were also evaluated for signs of complications including local anaesthetic systemic toxicity (an ASRA LAST checklist was available in the induction room).[20,21] Sixty minutes after "time 0", participants were asked to complete a "post-block" VAS score. The observer was asked to rate the ease of completing the case report form and the PI was called to indicate the end of data collection.

Monitoring, except BIS, was continued until the participant was moved to theatre. Success of the block (if performed) was recorded by using decreased ability to flex the elbow and decreased forearm sensation as measures. This was then indicated on the front of the case report form. Participants in whom the block was deemed to have failed would have been excluded from the study, but all blocks performed were successful.

At the end of the data collection, control participants were offered a supraclavicular block (or a patient-controlled analgesia pump) and all participants were offered general anaesthesia for their upper limb surgery, irrespective of the randomisation category they were allocated to. This was designed to ensure uniformity of the participant outcome postoperatively without impacting on fear for pain, anxiety and surgically-induced trauma. A detailed standard operating procedure for performing this pilot RCT is available as supplementary data.

Outcomes

Specific feasibility outcomes and criteria used to assess feasibility were generated as per CONSORT 2010 guidelines[12] and are shown in Table I.

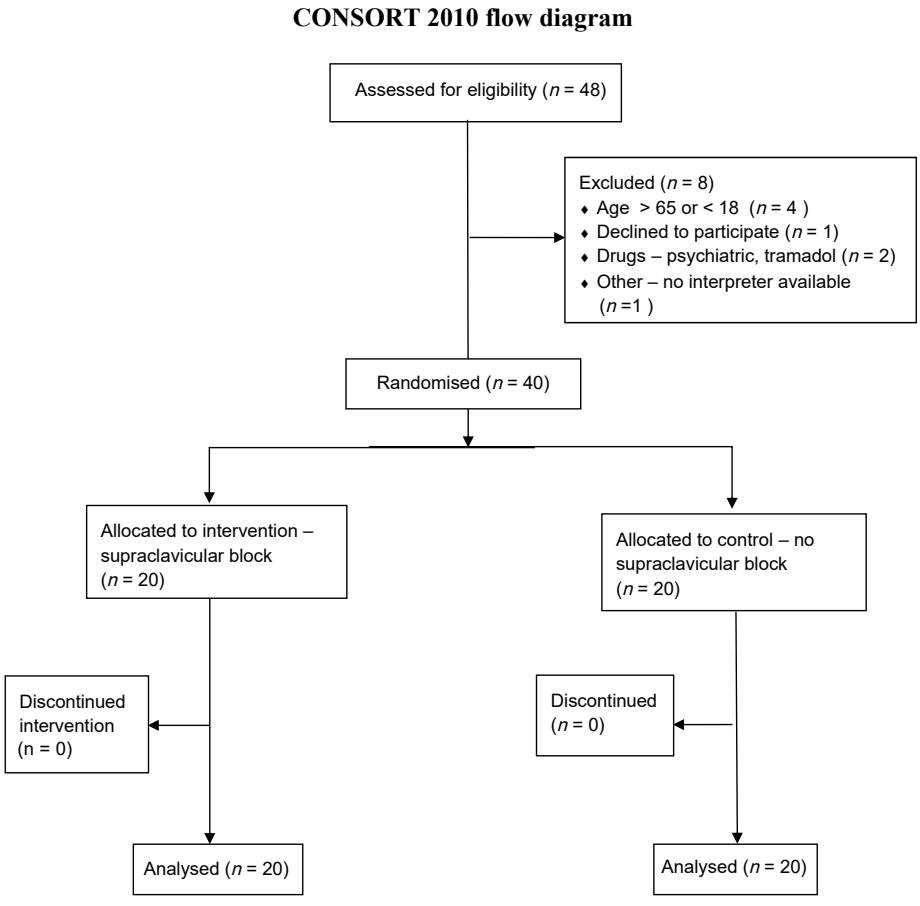

Figure 1: CONSORT flow diagram illustrating allocations of interventions

Data analysis

A complete list of variables collected, definitions of these variables and data dictionary for the case report forms are found in the supplemental data. Electronic data were captured and managed using REDCap electronic capture tools, hosted by Stellenbosch University.[22] REDCap data was exported to STATA version 15 (StataCorp, Texas, USA; 2017) for analysis. Sample size for the formal RCT were estimated using PASS version 12 software (Hintze; 2013; PASS 12, NCSS, LLC., Kaysville, Utah, USA; http://www.ncss.com).

Results

A total of 48 patients were screened for exclusion criteria and eight patients excluded (details of the recruitment are illustrated in Figure 1). Participant demographics are reported according to group in Table II. There were no statistically significant differences between the groups ($p > 0.05$), except for gender.

Regarding the primary outcomes, 41 of 48 (85.42%; 95% CI 71.62–93.46%) screened patients were invited to participate; and 40 of these 41 (97.56%; 95% CI 85.59–99.87%) participants accepted the invitation. The completion rate was 100% (95% CI 89.09–99.77%). In only four participants (10%; 95% CI 3.25–24.6%), the BIS electrodes needed to be replaced during the trial. There was inadequate contact (≥ 15% contact drop) in three participants (7.50%; 95% CI 1.96–21.48%). The median value for the opinion of "ease of completing data form" was five (37 of 40 answered "easy"; 92.50%), for "ease of collecting data" the median was five (37 of 40 answered "easy"; 92.50%) and the block success rate was 100% (95% CI 79.95–99.54%). The difference between BIS group means (per minute interval) showed all differences < 5 (Table III) with maximum differences at 24 minutes and around 50–55 minutes.

Reaching BIS < 80 was similar in both groups, where 85% reached < 80 in the block group and 75% in the no-block group (2-sided Fisher's exact test $p = 0.695$). Figure 2 illustrates the mean BIS values at each time interval and the total number of participants reaching BIS < 80 per time interval. Calculating the sample size needed to show a statistical difference of 10% using PASS version 12 software (Hintze; 2013; PASS 12, NCSS, LLC., Kaysville, Utah, USA; http://www.ncss.com) between groups in a formal RCT yielded a total of 500 participants (250 in each group).

Discussion

The aim of this pilot study was to determine the feasibility of conducting a formal RCT as well as executing the pilot trial in such a manner that it could be used as a template for a formal RCT in the future. Our results indicated that screening, recruitment, retaining, BIS electrode consumption and function, data collection and block success rate were all above cut-off values established for progression to formal RCT. The differences at each minute between group BIS means were < 5, the difference in incidence of BIS < 80 between groups was 10% and the sample size for a formal RCT was calculated to be 500 participants in total.

According to recently published literature regarding feasibility and pilot RCTs, our primary and secondary outcomes were appropriate for assessing whether we could progress to a formal trial.[23] In addition, all primary and secondary outcomes were planned and collected in line with recommendations from the CONSORT 2010 guidelines: extension to randomised pilot and feasibility trials.[12]

Although all primary outcomes relating to screening, acceptance, retaining, equipment, data collection and block success rate were met, our secondary outcomes were not positive. The difference between group mean BIS values and incidence of BIS < 80 did not meet our a priori criteria for progression to

Table II: Demographic data comparing intervention and control participants

Variable	Overall ($n = 40$)	Supraclavicular block (SCV)		
		Yes ($n = 20$)	No ($n = 20$)	*p*-value
Mean age in years (SD)	39 (13)	38 (14)	40 (11)	0.724*
Gender, *n* (%)				0.038†
Male	28 (70)	11 (55)	17 (85)	
Female	12 (30)	9 (45)	3 (15)	
Weight, kg (SD)	70 (14)	66 (15)	73 (13)	0.133*
Height, cm (SD)	168 (11)	167 (9)	170 (12)	0.399*
ASA Score, *n* (%)				0.507†
I	14 (35)	8 (40)	6 (30)	
II	26 (65)	12 (60)	14 (70)	
Chronic illnesses, *n* (%)				
Diabetes mellitus	2 (5)	1 (5)	1 (5)	1†
Hypertension	7 (17.5)	4 (20)	3 (15)	0.677†
COPD	1 (2.5)	1 (5)	0 (0)	0.311†
Other	22 (55)	12 (60)	10 (50)	0.525†

*t-test for independent groups, †X^2

ASA – American Society of Anesthesiologists, SCV – supraclavicular block, COPD – chronic obstructive pulmonary disease

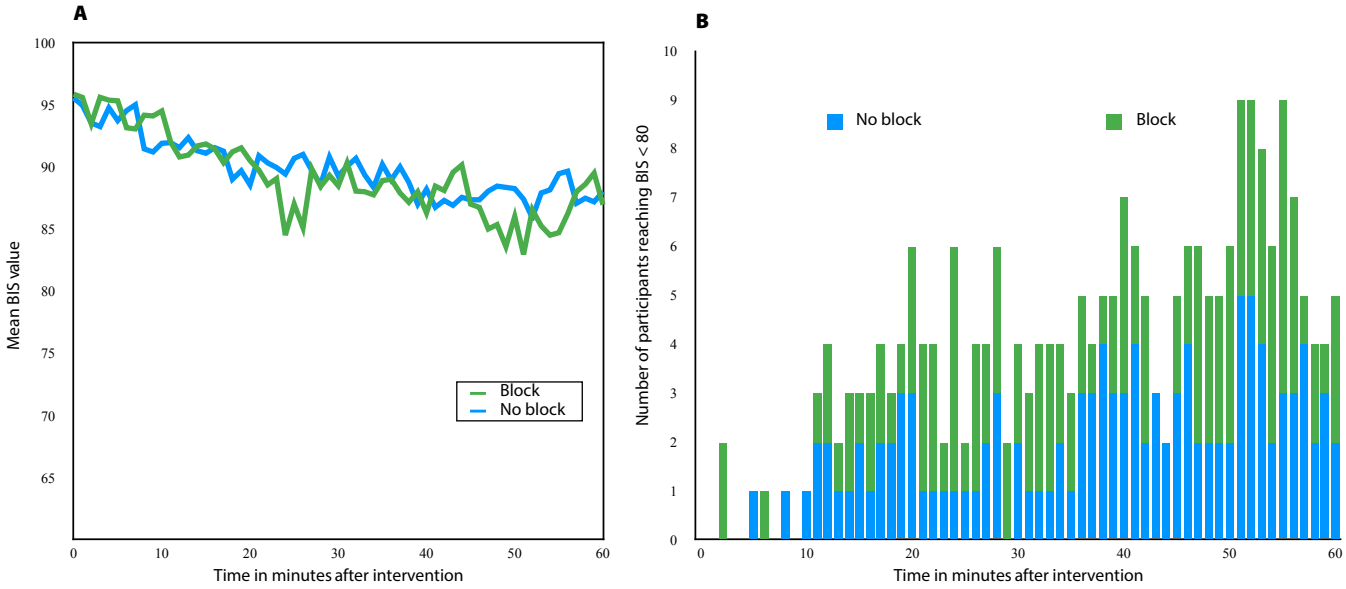

Figure 2: Comparison between treatment groups: (A) Mean BIS per time interval comparing participants who received block (green) to control participants (blue); (B) Stacked bar graph showing number of participants reaching BIS < 80 per minute interval and contributions of each treatment group (block = green, no block = blue)

Table III: Comparison of mean BIS values in 1-minute intervals after intervention

Time	SCV = Yes	SCV = No	Δ	Time	SCV = Yes	SCV = No	Δ
	BIS value (SD)	BIS value (SD)			BIS value (SD)	BIS value (SD)	
1	95.65 (2.621)	95.00 (4.301)	-0.65	31	90.37 (9.215)	90.11 (5.656)	-0.26
2	93.53 (7.933)	93.59 (4.744)	0.06	32	88.10 (10.326)	90.74 (5.905)	2.64
3	95.65 (3.801)	93.29 (5.108)	-2.36	33	88.05 (10.660)	89.40 (5.633)	1.35
4	95.42 (3.405)	94.81 (3.430)	-0.61	34	87.80 (12.129)	88.40 (6.295)	0.60
5	95.37 (3.804)	93.78 (4.989)	-1.59	35	88.95 (8.924)	90.25 (6.077)	1.30
6	93.20 (6.161)	94.58 (4.168)	1.38	36	89.05 (9.276)	89.00 (6.836)	-0.05
7	93.11 (5.032)	95.05 (3.252)	1.94	37	87.95 (9.550)	90.05 (7.251)	2.10
8	94.21 (4.328)	91.50 (6.856)	-2.71	38	87.20 (6.918)	88.80 (8.764)	1.60
9	94.15 (4.095)	91.25 (5.149)	-2.90	39	88.05 (7.287)	87.05 (9.113)	-1.00
10	94.55 (3.300)	91.95 (5.708)	-2.60	40	86.35 (8.487)	88.25 (8.201)	1.90
11	92.05 (6.074)	92.00 (6.859)	-0.05	41	88.50 (8.121)	86.80 (10.217)	-1.70
12	90.85 (7.809)	91.60 (6.954)	0.75	42	88.15 (8.067)	87.35 (9.713)	-0.80
13	91.00 (7.832)	92.40 (6.278)	1.40	43	89.61 (7.800)	86.95 (9.288)	-2.66
14	91.74 (7.408)	91.35 (6.667)	-0.39	44	90.20 (7.675)	87.60 (7.563)	-2.60
15	91.89 (9.374)	91.15 (6.753)	-0.74	45	87.05 (8.870)	87.40 (7.373)	0.35
16	91.50 (8.410)	91.60 (6.261)	0.10	46	86.79 (8.066)	87.40 (9.456)	0.61
17	90.39 (9.382)	91.32 (6.783)	0.93	47	85.05 (10.665)	88.10 (7.144)	3.05
18	91.26 (7.475)	89.05 (11.905)	-2.21	48	85.40 (10.908)	88.50 (6.493)	3.10
19	91.58 (6.611)	89.74 (7.302)	-1.84	49	83.63 (9.529)	88.40 (6.557)	4.77
20	90.56 (7.350)	88.60 (8.312)	-1.96	50	86.05 (11.083)	88.30 (6.642)	2.25
21	89.79 (7.656)	90.95 (8.127)	1.16	51	83.00 (10.954)	87.45 (9.960)	4.45
22	88.60 (8.580)	90.37 (7.243)	1.77	52	86.60 (10.287)	85.95 (8.401)	-0.65
23	89.11 (7.866)	90.00 (7.102)	0.89	53	85.30 (11.131)	87.95 (9.768)	2.65
24	84.56 (10.826)	89.47 (6.736)	4.91	54	84.55 (12.726)	88.20 (7.374)	3.65
25	87.05 (8.721)	90.74 (7.132)	3.69	55	84.75 (12.392)	89.50 (9.023)	4.75
26	89.67 (10.437)	91.05 (6.311)	1.38	56	86.26 (9.786)	89.70 (7.760)	3.44
27	89.89 (9.362)	89.75 (7.174)	-0.14	57	88.05 (8.810)	87.12 (10.173)	-0.93
28	88.47 (9.192)	88.63 (9.257)	0.16	58	88.65 (9.455)	87.53 (8.009)	-1.12
29	89.37 (8.770)	90.84 (5.824)	1.47	59	89.55 (9.128)	87.24 (10.449)	-2.31
30	88.53 (9.605)	89.32 (6.464)	0.79	60	87.00 (10.471)	88.07 (7.156)	1.07

BIS values are reported as mean values for all readings obtained, with SD in brackets
Δ – difference between means (no block - block), BIS – bispectral index, SCV – supraclavicular block, SD – standard deviation

formal RCT. At the same time, the new sample size estimation for formal RCT was 500 participants in total (> 300 cut-off value for progression to formal trial).

Since there is very little guidance available for developing quantitative thresholds that allow us to decide whether to continue with a larger trial,[24] the suggestion from CONSORT 2010 is to treat cut-off values as guidelines rather than strict values.[12] In our case, the cut-off values were based on local hospital experience, opinion and known feasibility study criteria.[13,14] The implication is that, even though our study team decided that a difference in mean BIS values between groups should be ≥ 10 and difference between incidence of BIS < 80 should be ≥ 20%, our findings of a 10% difference in incidence of BIS < 80 could be argued by some as being clinically important. Likewise, with enough resources and time, a sample size of 500 participants (as opposed to our cut-off of 300) may be feasible. The question we find ourselves asking is whether the findings of a larger trial would have significant implications in a real-world setting.

Considering that studies have been done to prove that the sedating effect of neuraxial anaesthesia is unlikely to be from high systemic levels of local anaesthesia[8] or rostral spread of local anaesthesia,[25] the most reasonable alternative is that decreased afferent input to the reticular activating system causes sedation.[4,11,25] It would then make sense to assume that a larger area of deafferentation (as with high volume spinal anaesthesia) would cause more sedation. The literature in support of this assumption, however, is conflicting, with some studies in support of high spinal levels causing sedation[10] and others claiming that sedation occurs regardless of height of block level.[7] If the extent of deafferentation has no bearing on sedation and non-neuraxial regional anaesthesia can indeed cause sedation, this may suggest an alternative mechanism and may even change sedation practice. In this light, a formal RCT with the new sample size of 250 participants in each treatment group (assuming that a difference of 10% in rate of BIS < 80 is clinically important) will be informative.

Positive aspects to carry forward from our study include the nature of the methodology (already designed for a formal RCT), positive screening, recruitment and completion rates, lack of difficulties with BIS electrodes, and easily collectable data. Specifically, collecting electronic BIS data in 1-minute intervals proved to be both effortless and a valuable source of information. There are, however, important limitations to this study.

One of these limitations is that the data on BIS values cannot be formally applied to a larger population as the sample size is small. The small sample size may also have influenced the difference between genders, although this may be due to other unknown factors. Regular blood pressure monitoring may also have influenced BIS readings by stimulating the participants and causing an increase in BIS value. This is unfortunately unavoidable as it is unethical to neglect monitoring after an anaesthetic intervention. Including emergency patients may have influenced BIS values as emergency patients are frequently starved for longer periods and may be more anxious.

Block success was defined as decreased sensation and decreased ability to flex elbow. Even though all intervention participants in this study had complete brachial plexus blockade, this definition of block success does not differentiate between a partial and complete block, which may have influenced BIS values. Block success was also only determined at the end of the study and time to onset of block may have influenced BIS values. The definition of block success will need to be further specified for future studies and consideration given to determining onset of complete block without disrupting the participant.

Time spent per study participant, from screening to completion, was roughly 90 minutes which may be problematic in a larger trial. In order to address this problem in a future trial, consideration needs to be given to the option of including multiple sites and numerous investigators. Furthermore, assessing the design of the trial should form part of a pilot trial,[14,23] yet our study did not include multiple sites and thus could not evaluate the feasibility of this aspect. Despite this fact, the evaluation of data collecting showed that it was uncomplicated and the forms were easy to complete. We believe that the thorough methodology and addition of a standard operating procedure form will simplify the conversion to a multi-site trial.

Conclusion

In this pilot trial, we showed that screening, recruitment and retaining strategies, anticipated BIS electrode complications, simplicity of data collection forms, and block success rates were adequately addressed to consider progression to a larger RCT. Although the study showed similar mean BIS values in treatment groups, there was a difference of 10% between groups in the incidence of BIS < 80 (indicating onset of sleep).[15] This difference is below our cut-off value for progression to formal RCT, yet may still be clinically significant. It may be preferable to assess the actual decrease in BIS value per patient, as this could be more clinically significant.

We propose that progression to a formal RCT is feasible **only** with the following modifications:

1. Decrease in BIS value from baseline should be measured per participant and clinically significant decrease should be estimated (we suggest a decrease of 10 or more).
2. Exclusion of emergency patients (starved for longer, more anxious, may affect BIS).
3. New sample size should be 500 participants with 250 in each treatment group.
4. Multi-site and various investigator involvement are recommended.

We also recommend that, should progression to a formal RCT be considered, there should be considerable consideration to whether such a trial would provide clinically useful information, and would justify the risks, patient discomfort and the considerable financial cost.

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orthopaedic theatres and the colleagues at the Department of Anaesthesiology and Critical Care at Tygerberg Hospital. Their assistance with the data collection for this study was invaluable.

Conflict of interest

The authors declare no conflict of interest.

Funding source

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Ethical approval

This trial was approved by local ethics board (HREC2 Stellenbosch University M19/05/014), registered with the National Health Research Ethics Council (NHREC 5358), the National Health Research Database (NHRD WC_201920_033), the South African National Trials Registry (SANCTR DOH-27-092021-7822), and the Pan African Clinical Trials Registry (PACTR PACTR202110574604922). The process for registering the initial trial in 2019 was via NHREC (proof of capture will be provided), prior to data collection. NHREC then fed trial information to SANCTR, which would then approve trial and send information on to PACTR. In 2020, this process was changed and the information was ported from one system to another, thus losing the original registration. Unfortunately, the research team only noticed this mishap in 2021 and thus had to re-register this trial retrospectively. For any further information and confirmation, please email Ms Sinazo Runeyi at: Sinazo.Runeyi@mrc.ac.za. This trial was conducted in line with all South African Good Clinical Practice guidelines.

ORCID

F Scannell https://orcid.org/0000-0002-2467-9279
T Esterhuizen https://orcid.org/0000-0002-8703-1664
R Naidoo https://orcid.org/0000-0002-8661-3646
S Chetty https://orcid.org/0000-0002-9878-5488

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