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REPORTS OF ORIGINAL INVESTIGATIONS

A novel approach of using brachial plexus blockade as an experimental model for diagnosis of intraoperative nerve dysfunction with somatosensory evoked potentials: a blinded proof-of-concept study

Une approche innovante utilisant le bloc du plexus brachial comme modèle expérimental pour diagnostiquer une dysfonction nerveuse peropératoire avec des potentiels évoqués somesthésiques : une étude de démonstration de faisabilité en aveugle

Jason Chui, MBChB · Alex Freytag, MD, FRCPC · Greydon Glimore, PhD · Shalini Dhir, MD, FRCPC · Max Rachinsky, MD, FRCPC · John Murkin, MD, FRCPC

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Abstract

Purpose *Intraoperative nerve dysfunction has been difficult to investigate because of its rarity and unpredictable occurrence. The diagnostic test attributes of nerve function monitors have not been clearly defined. This proof-of-concept study aimed to assess the feasibility of using brachial plexus blockade (BPB) in awake patients as an experimental model for nerve dysfunction to characterize the diagnostic test attributes of somatosensory evoked potentials (SSEPs).*

Methods *We obtained baseline SSEPs and neurologic function in patients and subsequently placed BPBs (experimental model) to generate progressive states of nerve dysfunction. We monitored SSEP changes (index test) and neurologic symptoms (reference standard) simultaneously during the onset of BPB to determine the temporal relationships and diagnostic test attributes of SSEPs.*

Results *Brachial plexus blockade produced differential motor and sensory dysfunction that allowed simultaneous clinical and neurophysiologic assessment. One hundred and fifty-seven pairs of multiple data points from 14 patients were included for final analysis. The onset of abnormal SSEP signals almost always preceded the onset of neurologic symptoms. The sensitivities and specificities of SSEP to detect the impairment of power (motor rating score $\leq$ 4/5), cold sensation, and two-point discrimination were 100% and 67%, 99% and 55%, and 100% and 46%, respectively.*

Conclusion *This study found that BPB can produce sufficient differential nerve dysfunction to allow adequate evaluation of the diagnostic test attributes of SSEPs as a nerve monitor. The results of this study may stimulate further work on refining intraoperative nerve dysfunction models and diagnostic nerve function monitors.*

This work has not been published previously except in abstract form at the Canadian Anesthesiologists' Society 2020 Annual Meeting, where it received the Ian White Patient Safety Award.

J. Chui, MBChB (✉)
Department of Anesthesia and Perioperative Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, C3-106, University Hospital, 339 Windermere Road, London, ON N6A 5A5, Canada
e-mail: Jason.chui@lhsc.on.ca

A. Freytag, MD, FRCPC · S. Dhir, MD, FRCPC · M. Rachinsky, MD, FRCPC · J. Murkin, MD, FRCPC
Department of Anesthesia and Perioperative Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada

G. Glimore, PhD
Department of Clinical Neurological Science, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada

Trial registration *www.clinicaltrials.gov (NCT03409536); registered 24 January 2018.*

Résumé

Objectif *La dysfonction nerveuse peropératoire est difficile à étudier en raison de sa rareté et de son imprévisibilité. Les attributs d'un test diagnostique des moniteurs de la fonction nerveuse n'ont pas été clairement définis. Cette étude de démonstration de faisabilité visait à évaluer la faisabilité de l'utilisation d'un bloc du plexus brachial (BPB) chez des patients éveillés comme modèle expérimental de la dysfonction nerveuse afin de caractériser les attributs de test diagnostique des potentiels évoqués somesthésiques (PES).*

Méthode *Nous avons enregistré les PES et la fonction neurologique de base des patients, puis administré des BPB (modèle expérimental) pour générer des états progressifs de dysfonction nerveuse. Nous avons surveillé simultanément les changements des PES (test pour déterminer l'indicateur) et les symptômes neurologiques (norme de référence) pendant l'évolution du BPB afin de déterminer les relations temporelles et les attributs de test diagnostique des PES.*

Résultats *Le bloc du plexus brachial a produit une dysfonction motrice et sensorielle différentielle qui nous a permis de procéder à une évaluation clinique et neurophysiologique simultanée. Cent cinquante-sept paires de points de données multiples issues de 14 patients ont été incluses pour l'analyse finale. L'apparition de signaux de PES anormaux a presque toujours précédé l'apparition de symptômes neurologiques. Les sensibilités et les spécificités des PES pour détecter la perte de force (score moteur ≤ 4/5), la sensation de froid et la discrimination à deux points étaient de 100 % et 67 %, 99 % et 55 %, et 100 % et 46 %, respectivement.*

Conclusion *Cette étude a constaté que le bloc du plexus brachial peut produire une dysfonction nerveuse différentielle suffisante pour permettre l'évaluation adéquate des attributs de test diagnostique des PES en tant que moniteur nerveux. Les résultats de cette étude pourraient motiver d'autres travaux sur l'amélioration des modèles de dysfonction nerveuse peropératoire et des moniteurs diagnostiques de la fonction nerveuse.*

Enregistrement de l'étude *www.clinicaltrials.gov (NCT03409536); enregistrée le 24 janvier 2018.*

Keywords evoked potential · brachial plexus blockade · SSEP · peripheral nerve injuries · diagnostic tests

Peripheral nerve dysfunction is one of the most perplexing perioperative complications that continues to result in patient disability and malpractice claims.[1] The use of a nerve monitor to detect and mitigate intraoperative nerve dysfunction is theoretically compelling. Nevertheless, intraoperative nerve dysfunction has been difficult to investigate clinically because of the rarity and unpredictability of its occurrence. This methodological challenge greatly hampers the development of an effective intraoperative monitor and preventative measures.[1]

Somatosensory evoked potential (SSEP) monitoring has been employed intraoperatively to detect nerve dysfunction,[2–9] assess the completeness of nerve repair,[10] and guide peripheral nerve decompression.[11] Despite these routine uses, the relationship between abnormal SSEPs and the severity of neurologic injury (or clinical symptomatology) has not been clearly defined. One fundamental limitation to showing such a relationship is that intraoperative SSEP monitoring is used in patients under general anesthesia, which precludes the possibility of real-time direct correlation between abnormal SSEPs and the presence and severity of adverse neurologic outcomes. Thus, previous studies have used postoperative neurologic function as a reference standard.[12] In clinical practice, a rescue intervention is often applied when an abnormal SSEP signal develops before the postoperative neurologic assessment (i.e., reference standard) is employed, resulting in a potential misclassification bias.[12] Additionally, assessment of SSEP in awake patients is often challenging because of patient discomfort during peripheral nerve stimulation and significant muscle artefacts.

To circumvent these methodological issues, we hypothesized that brachial plexus blockade (BPB) in awake patients can function as an experimental model to produce differential states of nerve dysfunction during block onset that allow real-time correlation between abnormal nerve conduction and clinical symptomatology. We conducted a proof-of-concept study to evaluate the feasibility of using the BPB model to assess the diagnostic test attributes of SSEPs to detect nerve dysfunction and define its diagnostic test attributes.

Methods

Study design

We conducted a prospective proof-of-concept cohort study to evaluate the feasibility of using BPB as an experimental model of nerve dysfunction to assess the diagnostic test attributes of SSEPs. The study protocol was approved by the institutional Research Ethics Board at Western University, London, ON, Canada (# 108778). Written informed consent was obtained from all participants. The

study was conducted at a single tertiary referral centre, St Joseph's Hospital, London, Ontario, Canada. As part of this proof-of-concept study, we dedicated a planned pilot phase between March and December 2017 to programming, identifying, and addressing technical issues, and preliminary patient testing. After confirming technical feasibility to proceed with the main study, we registered the protocol at www.clinicaltrials.gov on 24 January 2018 (NCT03409536). Patients were enrolled for the main study from 30 January to 8 June 2018. We undertook post hoc data processing and analyses from July 2018 to December 2019.

Participants

We included adult patients aged 18 yr or older undergoing elective upper limb surgery and scheduled to receive a BPB. Participants were excluded if they i) were unable to perform the tasks associated with a complete neurologic examination (e.g., because of dementia or upper limb fracture), ii) refused to participate or were unable to provide informed consent, iii) had contraindications for SSEP monitoring (e.g., skin lesions on the stimulation or recording sites), or iv) had known pre-existing peripheral neuropathy or brachial plexus injury.

Target condition and experimental model

The target condition was intraoperative peripheral nerve dysfunction. We used BPB to produce pharmacologically induced nerve dysfunction as an experimental model for intraoperative nerve dysfunction. In awake patients, BPB is an attractive model because it provides a transient and progressive de-afferentation state of peripheral nerves (mimicking a range of nerve dysfunction over time from normal, to mild, to severe, to complete dysfunction) and allows for real-time assessment of the relationship between clinical symptoms and SSEP changes. It also overcomes research limitations due to the random nature and low incidence of intraoperative peripheral nerve dysfunction. The side and approach of BPB (e.g., supraclavicular or infraclavicular) were not restricted because the experimental model was used to mimic different severities and patterns of nerve dysfunction in clinical practice. For the same reason, the doses, concentrations, volumes, and use of adjuncts of the local anesthetics were not restricted.

Index test

The index test was subcortical SSEP, recorded with the use of EPAD® (SafeOp Surgical, Hunt Valley, MD, USA). The EPAD® is a simplified evoked potential monitoring device that shares the same electrophysiologic principles as conventional intraoperative neurophysiologic monitoring machines. We used this device for this study because i) surface adhesive electrodes rather than needle electrodes are used for both stimulation and recording, which is suitable for awake patients in this study setting, ii) it consists of a newly patented artifact rejection system that might potentially improve SSEP signals in awake patients, iii) it can display and store raw SSEP data permitting more detailed post hoc processing and analysis, and iv) it can be used to detect peripheral nerve injury.[13,14]

The subcortical SSEP was obtained by stimulating the ulnar and median nerves at the wrist level of the operative arm and recorded at the fifth cervical spine level (C5) with a reference electrode placed on the forehead (Fz). The pre-set stimulation frequency was 4.7 Hz with a 300-μsec pulse initially set at 10–20 mA and sequentially increased until the patients complained of discomfort. The signal averaging was set at 300 cycles. The raw SSEP data were downloaded and stored at the end of each case for subsequent off-line post hoc analysis.

Reference standard

The reference standard test was a neurologic examination of motor power, cold sensation, and two-point discrimination of the operative arm by an independent outcome assessor. The details of the neurologic examination are described in the Appendix. Power was assessed using the motor rating score (MRC) on a scale of 0 to 5. The power of the median nerve was tested by thumb abduction and the power of the ulnar nerve was tested by finger abduction. Sensory examination of the median nerve was assessed on the skin of the palmar side of the thumb/palm and the ulnar nerve was assessed on the skin of the fifth digit/medial palm. Cold sensation was assessed as present or absent after ice was applied to the skin of the assessed area. Two-point discrimination was assessed using a two-point discrimination esthesiometer (measured in mm).

Study procedure

After informed consent was obtained, a blinded independent outcomes assessor performed a baseline neurologic examination in the "Block Room" before the BPB was placed. The neurologic examination was performed as described above and in the Appendix. After baseline SSEP recordings were established, a single-injection BPB was performed as per clinical routine to achieve complete sensory and motor blockage with an onset time of approximately 30 min. The outcomes assessor reassessed the patients' sensory (two-point

discrimination and cold sensation) and motor function every five minutes for up to 30 min during the onset of the block and SSEPs were recorded concomitantly until either complete sensory and motor blockage or for up to 30 min after BPB. The SSEP recording was interrupted every five minutes during the onset of the BPB to facilitate the neurologic assessment. The monitor screen of the SSEP machine was covered by an opaque plastic sheet so that the assessor was blinded to the SSEP readings.

Sample size

We identified no previous studies to guide a sample size calculation. Because of this and the proof-of-concept nature of this study, our approach to sample size projection was largely based on enrolling a sample size of convenience. We designed our study to provide a maximum of 14 data point pairs from seven assessment time points of median and ulnar nerve distribution per patient. We estimated that a minimum of 150 data point pairs (i.e., approximately ten to 11 patients) would be required to assess the diagnostic test attributes of SSEPs with a 95% confidence interval (CI) width of 20% for a disease prevalence of 85–95%, expected sensitivity of 95%, and expected specificity of 60%. Nevertheless, we anticipated that we might not be able to perform seven time point assessments in all patients within 30 min. We also expected a high exclusion rate due to patient discomfort from intolerable nerve stimulation and muscle artefacts, especially from neck and paraspinal muscle contraction in awake patients. Therefore, we projected a sample size of convenience of 40 patients to account for these factors.

Post hoc processing of raw SSEP signals

In the post hoc raw SSEP data analysis, we custom built a graphical user interface using PySide (version 1.2.4) and Python (version 3.6.5) software (Python Software Foundation, Wilmington, DE, USA) to analyze the raw data. This interface allowed us to perform post hoc adjustment of the sample frequency, high-pass and low-pass filters, filter order, threshold, and number of averaging. The C5 EEG data were sampled at 10,000 Hz. The raw data were detrended and divided into 50-msec segments, using the time of stimulation as the zero point. Segments were averaged and a second order Butterworth filter was applied to remove electromyographic (EMG) activity. The typical setting of the SSEP bandpass was 30–1 kHz. In our analysis, we sequentially increased the high-pass filter (10 Hz each time from 30 Hz to 250 Hz) until muscle (or EMG) artifacts were satisfactorily removed. This increase of the high-pass filter range to remove motion artifacts from monitoring signals is one of the recommended strategies to improve SSEP signal quality in a recent guideline.[15] The number of repetitions to be averaged ranged between 200 and 400 to allow an interpretable and reproducible SSEP signal. For each patient data set, after the optimal baseline SSEP signal was determined, the setting was kept constant during subsequent analysis to avoid erroneous changes in the responses due to the changes in filter setting.

Statistical analysis

We used descriptive statistics to summarize patient baseline and regional nerve block characteristics. The experimental feasibility of the BPB model was assessed by how adequately the data points determined the diagnostic test attributes of SSEPs. To calculate the diagnostic values of subcortical SSEPs, we defined the following target conditions as binary data (yes or no): impairment of motor power as MRC $\leq$ 4/5, impairment of cold sensation if the study participant failed to feel the ice, and impairment of two-point discrimination if the study participant failed to discriminate the baseline two-point distance after block. A positive index test was defined as complete loss of SSEP signal. Each pair of SSEPs and clinical assessment was considered as one independent state of nerve dysfunction. We constructed 2 x 2 tables to determine the diagnostic test attributes of subcortical SSEPs in detecting impairment of motor power, cold sensation, and two-point discrimination. The sensitivity, specificity, positive and negative predictive values, and area under the receiver-operating-curve (ROC) were calculated. To account for the effects of clustered data due to correlation between observations within each patient, sensitivity and specificity were adjusted using the variance adjustment method.[16] We plotted the proportion of participants over time with a positive reference test (loss of neurologic function) *vs* a positive index test (loss of subcortical SSEP signal) to define the temporal relationship of SSEPs and corresponding neurologic changes. We used STATA (version 14; StataCorp LP, TX, USA) for the statistical analyses.

Results

Following provision of written informed consent, 40 patients were assessed for eligibility and enrolled, of which 14 were included in pilot programming and testing and 26 in the main study. Of the 26 patients included in the main study, 12 were excluded, six because of inadequate intensity of peripheral nerve stimulation to sufficiently evoke subcortical SSEP responses, two because of significant muscle artefacts that precluded reliable SSEP waveform interpretation, three because of insufficient time

available to perform SSEP monitoring and physical assessment before the scheduled surgery, and one because of technical errors during data downloading. Fourteen of the 26 (54 %) patients in the main study yielded sufficient SSEP recordings. One hundred and fifty-seven pairs of multiple data points from these 14 patients were included in the final analysis; each patient provided an average of 11 pairs of data points. Figure 1 shows a study participant flow chart. Tables 1 and 2 summarize patient baseline and regional nerve block characteristics. All patients received a small dose of midazolam during the regional block to improve comfort, and all patients were able to undergo the neurologic assessment.

Figure 2 depicts the temporal relationship between loss of neurologic function and subcortical SSEP test positivity (i.e., loss of SSEP signals) over 0 to 30 min after BPB placement. The majority (88%) of patients had complete loss of subcortical SSEP signals 5 min after the regional nerve block was performed. Nevertheless, approximately half of the patients had impairment in power ($\leq$ 4/5), cold sensation, and two-point discrimination at the same time (57%, 46%, and 43%, respectively). There was a consistent pattern, which showed that loss of subcortical SSEP signals preceded the impairment of power ($\leq$ 4/5), followed by impairment of cold sensation, and then impairment of two-point discrimination over 30 min after BPB onset (Fig. 2). Because of this rapid complete loss of subcortical SSEPs and the time lag for averaging subcortical SSEPs, further analysis of amplitude and latency changes over time was not feasible.

Table 2 summarizes the diagnostic test attributes of subcortical SSEPs to determine peripheral nerve dysfunction. Subcortical SSEPs were almost equally sensitive in detecting the impairment of power (MRS $\leq$ 4/5) (mean 100%; 95% CI, 100 to 100), cold sensation (mean 99%; 95% CI, 97 to 100), and two-point discrimination (mean 100%; 95% CI, 100 to 100), and resulted in very high negative predictive values (mean 100%, 95% CI, 88 to 100; mean 97%, 95% CI, 82 to 100; and mean 100%, 95% CI, 88 to 100, respectively). Subcortical SSEPs were only moderately specific in confirming the impairment of power (MRS $\leq$ 4/5) (mean 67%; 95% CI, 53 to 82), cold sensation (mean 55%; 95% CI, 41 to 67), and two-point discrimination (mean 46%; 95% CI, 34 to 58%), respectively, and resulted in moderate positive predictive values (mean 89%, 95% CI, 82 to 94; mean 82%, 95% CI, 74 to 88; and mean 73%, 95% CI, 65 to 81, respectively). The overall diagnostic values of subcortical SSEPs, as reflected by the area under ROC curves, were 84% (95% CI, 77 to 90) for diagnosing impairment of power (MRS $\leq$ 4/5), 77% (95% CI, 70 to 83) for cold sensation, and 73% (95% CI, 67 to 79) for two-point discrimination.

The intraclass correlation coefficients of impairment of power (MRS $\leq$ 4/5), cold sensation, and two-point discrimination were 0.23, -0.02, and 0.07, respectively. The adjusted specificities were 67% (95% CI, 52 to 83) for impairment of power (MRS $\leq$ 4/5), 55% (95% CI, 41 to 68) for cold sensation, and 46% (95% CI, 33 to 59) for two-point discrimination. The sensitivities remained unchanged after adjustment for the clustered data effect.

Discussion

The present proof-of-concept study found that our BPB model can be used to produce differential states of motor and sensory dysfunction that allow adequate assessment of

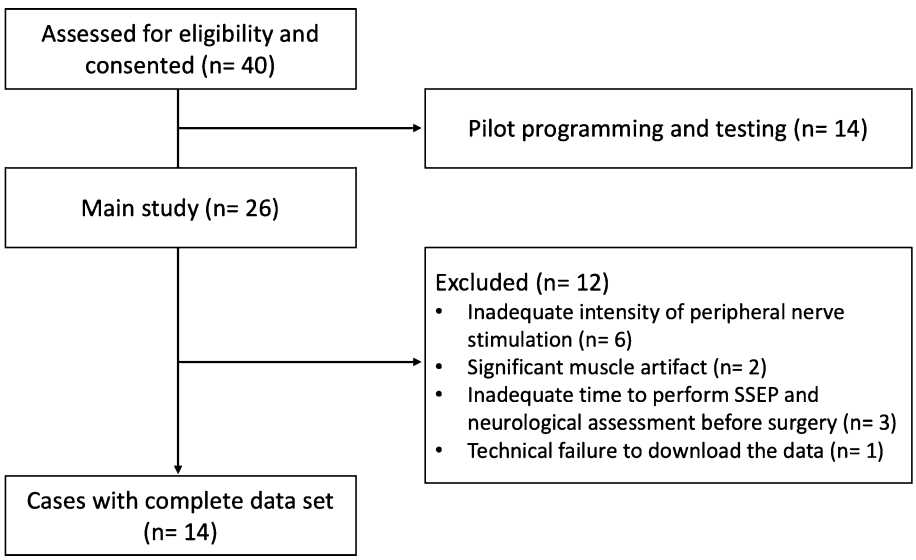

Fig 1 Study flow diagram.

Table 1 Patient baseline characteristics and details of brachial plexus blockade

Characteristic	Value (N = 14)
Age, mean (SD)	50 (12)
Female, *n*/total *N* (%)	6/14 (43)
Body weight (kg), mean (SD)	85 (13)
Height (cm), mean (SD)	172 (8)
BMI ($kg \cdot m^{-2}$), mean (SD)	28.6 (3.4)
Right-handed, *n*/total *N* (%)	13/14 (92)
Hypertension *n*/total *N* (%)	4/14 (29)
Diabetes mellitus, *n*/total *N* (%)	0/0 (0)
Peripheral vascular disease, *n*/total *N* (%)	0/0 (0)
Side of regional block (left/right) (*n*)	4/10
Type of brachial plexus block (*n*)	Supraclavicular: 3
	Infraclavicular: 7
	Axillary: 4
Volume of 0.5% ropivacaine (mL),* mean (SD)	36 (8)
Dose of midazolam (mg), mean (SD)	1.7 (0.5)

*All patients received 0.5% ropivacaine for brachial plexus blockade except one who received a mixture of 20 mL 0.5% ropivacaine and 20 mL 1.5 % lidocaine.

SD = standard deviation.

Table 2 Diagnostic test attributes of subcortical SSEP in iatrogenic peripheral nerve dysfunction

Reference test	TP	FP	TN	FN	LR+	LR-
Loss of two-point discrimination	94	34	29	0	1.85	0
Loss of cold sensation	105	23	28	1	2.20	0.02
Power (MRS $\leq$ 4/5)	114	14	29	0	3.07	0

FN = false negative; FP = false positive; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; MRS = Motor Rating Score; TN = true negative; TP = true positive.

the diagnostic test attributes of a nerve monitor. Many participants dropped out because of intolerable stimulation and motion artefacts of performing SSEPs in awake patients. In anticipation of this challenge, we had projected our sample size accordingly to provide sufficient data to determine the diagnostic test attributes of SSEPs. Our observations suggest that BPB can be used as an experimental model to overcome methodological and practical challenges of studying nerve dysfunction.

A number of studies in the 1980–1990s reported on the use of upper arm tourniquet application, direct compression, or direct occlusion of the brachial artery to induce ulnar nerve ischemia for investigating SSEP responses under ischemic conditions.[17–20] All of these studies only showed that SSEPs could be abolished under ischemia; none aimed to assess the temporal relationships between SSEPs and clinical symptomology or the diagnostic test attributes of SSEPs. The iatrogenically induced nerve ischemia model has the advantage of being more related to the actual mechanism of perioperative nerve injury; however, this method may cause harm to study participants. Volunteers in one of these earlier studies[17] reported significant discomfort after prolonged periods of tourniquet application. We expected difficulties obtaining ethical permission to use this ischemic model because of current human research ethics standards and patient expectations. Furthermore, most participants in this particular study[17] neither developed complete paralysis/numbness nor complete abolishment of SSEP signals, even after prolonged periods of tourniquet application. This implies that the tourniquet ischemic model cannot consistently produce complete differential states of sensory and motor dysfunction and therefore is not adequate for comprehensive assessment of the diagnostic test attributes of a nerve monitor.

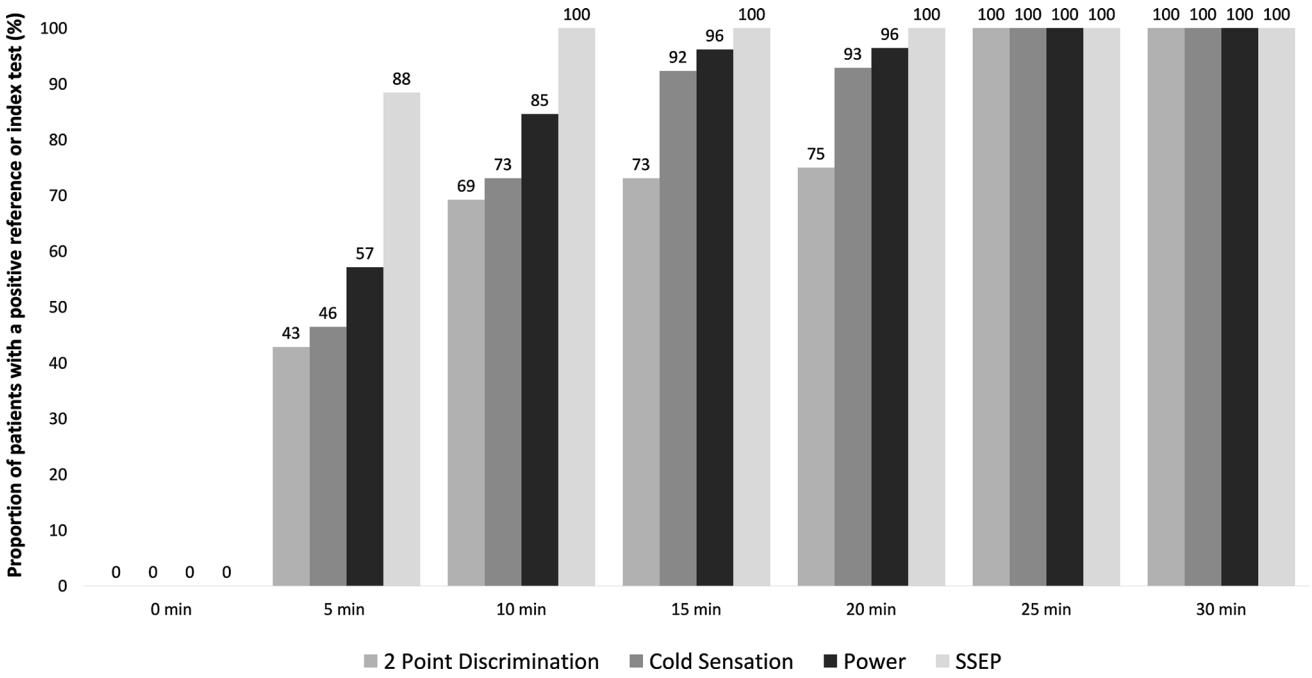

Fig 2 Proportion of participants over time with a positive reference *vs* index test 0 to 30 min after brachial plexus blockade. A positive index test was defined as the complete loss of somatosensory evoked potential (SSEP) signal. A positive reference test was defined as impairment of two-point discrimination (failure to discriminate the baseline two-point distance), impairment of cold sensation (failure to feel ice), or impairment of motor power (motor rating score [MRS] $\leq$ 4/5). At each time point of assessment, the proportion of participants with a positive index test was higher than that with a positive reference test. The graph illustrates the observation of a pattern whereby loss of SSEP signals tended to precede the onset of impairment of power (MRS $\leq$ 4/5), followed by impairment of cold sensation, and impairment of two-point discrimination.

The present study also yielded two secondary findings related to the diagnostic test attributes of SSEP. First, we observed a consistent temporal relationship between abnormal SSEPs and clinical symptomatology; the neurophysiologic derangement on SSEPs almost always preceded the onset of clinically apparent motor and sensory dysfunction. This suggests that loss of subcortical SSEPs, representing a neurophysiologic impairment, occurs before the onset of any clinically apparent neurologic deficits. Second, SSEP had a very high sensitivity with an almost non-existent false negative rate for detecting peripheral nerve dysfunction. These results are largely in concordance with the current understandings of the diagnostic test attributes of SSEPs.[2–9,21,22]

The results of this study also support intraoperative identification of abnormal sensory nerve conduction by SSEPs to detect an insult that impacts/could impact the peripheral nerve. As SSEPs are transmitted through sensory fibres in peripheral nerves, abnormal SSEPs reflect the integrity and functionality of the sensory nervous structures. Nevertheless, the brachial plexus is a mixed sensory and motor nerve structure; thus, the possibility of an isolated peripheral motor nerve injury with preserved SSEP signals is highly unlikely in the clinical setting. Additionally, previous studies did not report any concerns of differential efficacy of SSEPs in preventing damage to sensory and motor fibres in a peripheral nerve.[2–8,23,24] In the current study, SSEPs had similar diagnostic value in detecting sensory and motor deficits. This finding supports the contention that SSEPs can reflect the integrity and functionality of the peripheral motor fibre given that the most insult to a peripheral nerve causes damage to both sensory and motor fibres simultaneously. In contrast, there is a valid concern that the use of SSEPs may miss isolated motor tract (corticospinal tract) injury during spine surgery.[25,26]

Limitations and strengths

One major limitation of this study is that the proof-of-concept nature of this research was associated with inherent technical challenges that mandated an adaptive approach with pilot testing and programming prior to the main study. A high proportion of the enrolled patients were excluded because of intolerable stimulation and motion artefacts. This may improve with better patient preparation through provision of incentives as some neurophysiologic laboratories are able to routinely perform SSEPs in awake

patients. Nevertheless, our sample size was projected to account for such a high dropout rate. It is important to mention that the high dropout rate was related to the use of SSEPs (the index test assessed in this study) rather than the experimental (BPB) model itself. The applicability of using the BPB model to study other nerve monitors that do not require the painful nerve stimulation is expected to be higher.

Second, the temporal resolution was limited to five minutes because i) SSEPs require an average of 300–500 cycles to produce one averaged SSEP signal (approximately two to three minutes) and ii) performing a simultaneous physical examination of corresponding dermatomes and myotomes takes two to three minutes. Thus, five minutes is the shortest time frame (or highest temporal resolution) that we can achieve clinically. This time limitation also precluded us from performing more detailed quantitative measurements of motor and sensory function such as hand grip. One potential modification of the current model is to use a lower dose or divided doses (via indwelling perineural catheter) of local anesthetics to allow slower onset of the BPB, thereby yielding more data points for each patient.

A strength of this study is the innovative study design, which overcomes several methodological issues seen in past studies. First, our study eliminates misclassification bias as the experimental model allows for real-time correlation. Second, by using a predictable pharmacologically induced nerve dysfunction model in patients undergoing BPB for surgery, we were able to eliminate the requirement of a large-sample size human study. Nerve injury could be induced in an animal model, but this would not provide real-time correlation with neurologic symptoms as in the present study because the animal could not readily indicate motor and perception changes such as temperature. Furthermore, volunteers would not agree to receive an irreversible iatrogenic nerve injury for a research study nor would this be ethical, thereby making our model of nerve dysfunction the most accurate based on feasibility and ethical standards. Third, we were able to consider a high inter-individual variability of normal SSEP values. Our current diagnostic criteria of abnormal SSEPs are individualized and based on relative reduction from baseline SSEP values. Previous studies[21] on patients who had previous nerve injuries could only use the SSEP values of the contralateral arm as baseline rendering that study design suboptimal because there is a significant difference in SSEP values between two arms in normal subjects.[21] Lastly, the concept of using BPB as an experimental model is novel. Few studies [22,27–30] have investigated the use SSEP as an endpoint measure to quantify the onset and completeness of peripheral nerve and neuraxial blockade; however, none of these studies have discussed the use of BPB as an experimental model to study nerve dysfunction, nor did these report diagnostic accuracy of a nerve monitor.

Generalizability

An important question is whether the present diagnostic test attributes determined by a pharmacologically induced nerve dysfunction model are applicable to the clinical target condition of intraoperative peripheral nerve damage. The mechanism of pharmacologically induced nerve dysfunction is the reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane, whereas most anatomical nerve damage is due to stretching, compression, and ischemia. It is important to clarify that the function of a nerve monitor is to detect nerve dysfunction rather than to differentiate the underlying mechanism. As such, the current diagnostic criteria defining abnormal SSEPs (i.e., based on changes in amplitude and/or prolongation of latency) are employed independent of the mechanism of injury (e.g., stretching, transection, or ischemia). The current reported diagnostic test attributes of evoked potential monitoring are non-specific to any mechanism of injury. As intraoperative nerve dysfunction is often multifactorial[1]; no single experimental model can include and represent all possible causes and combination of nerve dysfunction. Thus, while it is unknown how the specific mechanisms of nerve dysfunction alter the diagnostic test attributes of a nerve monitor, the diagnostic test attributes determined by the present pharmacologically induced nerve dysfunction model still provide important insight into the clinical application of SSEPs.

Since this study only focused on the diagnostic test attributes of subcortical SSEPs on peripheral nerve dysfunction, our results might not be directly applicable to spinal cord injury or cerebral injury. A further study with a similar study design on patients receiving spinal anesthesia (neuraxial blockade) as a model of differential states of spinal cord dysfunction may provide more information on the diagnostic test attributes of lower limb SSEPs for use in spinal cord injury. Moreover, the present study employed subcortical SSEPs (N13), so our results might not be applicable when cortical SSEPs (N20) are used. Nevertheless, a previous study[21] on patients with traumatic brachial plexus injury reported that subcortical SSEPs (N13) were most closely related to the severity of the lesion than cortical SSEPs (N20). Lastly, as volatile agents and propofol have minimal suppressive effects on subcortical SSEPs,[31] the results of this study are likely generalizable to the patients under general anesthesia.

Conclusion

The findings of the present proof-of-concept study suggests that BPB in awake human patients can be used as a model to produce a differential state of peripheral nerve dysfunction that largely overcomes previous methodological limitations and allows comprehensive assessment of the diagnostic test attributes of a nerve monitor. A major caveat of the BPB model is whether the results are generalizable to other types of nerve injury. The large dropout rate related to intolerable stimulation of SSEP requires careful attention in future studies. The experience of this study may stimulate further work on refining models and monitoring and improve the understanding of peripheral nerve injury.

Author contributions *Jason Chui* contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. *Jason Chui* and *John Murkin* contributed to the study conception and design. *Alex Freytag*, *Shalini Dhir*, and *Max Rachinsky* contributed to the acquisition of data. *Jason Chui* and *Greydon Glimore* contributed to the analysis of data. *Jason Chui*, *Greydon Glimore*, *Shalini Dhir*, and *John Murkin* contributed to the interpretation of data. All those designated as authors meet the criteria for authorship as defined by the ICMJE recommendations.

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Appendix: Study procedure of the neurologic examination

The neurologic examination was performed by the same independent outcome assessor using the same instructionS as follows:

1. Motor score

We used MRC scale to assess motor power. Medial nerve power was tested by thumb abduction. Ulnar nerve power was tested by finger abduction.

MRC scale

Grade	Description
5	Normal power
4	Active movement against gravity and resistance
3	Active movement against gravity
2	Active movement with gravity eliminated
1	Flicker or trace of contraction
0	No contraction

2. Cold sensation

1. The outcome assessor explained and showed the procedure with his/her eyes open. The outcome assessor applied ice to the study participant's forehead and followed by to the hand to inform the study participant about the cold sensation of ice.
2. The study participant was asked to close his/her eyes.
3. The outcome assessor applied the ice or a gauze at room temperature on the skin of the area of testing. "I am going to touch your hands. Please tell me whether it is 'cold' or 'not cold'."

3. Two-point discrimination test.

Equipment: Two-point discrimination esthesiometer.

Testing procedure

1. The outcome assessor explained and showed the procedure before starting the assessment. The outcome assessor asked the study participant to open his/her eyes during the demonstration. For example, "I am going to use this instrument to touch your hands or arms. It will be either one or two points. Please tell me if you feel one or two points when you feel the touch."
2. The outcome assessor assessed and ensured the understanding of the procedure.
3. The study participant was asked to close his/her eyes.
4. The outcome assessor began the test with the points of the anesthesiometer opened and ensured the stimulus was light and equal pressure across the two points.
5. The outcome assessor moved the two points closer together across consecutive trials until the study participant cannot distinguish the two points as separate.
6. The outcome assessor measured the distance between the two points using the esthesiometer ruler.

MRC = Motor Rating Score.

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