Protocol

Title: Comparison of Ultrasound Guided Supraclavicular Brachial Plexus Block with and without Peripheral Nerve Stimulation (PNS) Guidance: A randomized controlled trial.

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INTRODUCTION

Peripheral Nerves Blockade (PNB) via local anaesthetics is a method of providing anesthesia and analgesia to the limbs and it was well established in the late 20th century. However, it did not come very well into practice because of unreliability, high rate of complications and failure due to lacking of accurate and reliable techniques of nerve localization at that point in time(1). It was only when newer nerve localization methods, such as Peripheral Nerve Stimulation (PNS) and Ultrasound (U/S) Imaging started becoming commercially available that the trend of Regional Anaesthesia started getting recognized among the physicians. PNB as a sole anaesthesia technique for limb surgery took further integration in practice and widespread acceptance among anaesthetist in the last decade, once ultrasound technology advanced to newer heights resulting in compact and more mobile units, higher resolution, needle recognition software etc.

When compared to PNS guided regional anaesthesia (PGRA), ultrasound guided regional anaesthesia (UGRA) offers a number of important practical advantages such as direct real-time visualization of the anatomy of interest, needle pathway and its passing through structures and spread of local anaesthetic, and the potential for instantaneous needle re-adjustments as per need (2). All this allows for safer and more effective distribution of local anaesthetic in the region of desired peripheral nerve (3). This superiority of Ultrasound Guidance led to fade in the use of PNS guidance in the Regional Anaesthesia practice over the recent years.

Regardless of the previously discussed superiority of U/S Guidance in Regional anaesthesia (RA), it has its own limitations. Such limitations include difficulty in visualization and identifying neural structures when they are lying far away from the skin either due to thick overlying subcutaneous adipose tissue in the obese patients or simply because of the presence of nerve bundle in the deeper tissue planes, and inability to confidently identify and exclude the placement of needle tip within the nerve, where if an injectate is injected will lead to nerve damage (4).

Such limitations of U/S Guidance in RA can be circumvented by using PNS Guidance in its conjunction. PNS works by delivering a small pulse of electric current through the needle tip which when in close proximity to a neural structure will lead to its stimulation and its respective muscle contraction, thereby helping us in identifying the neural structure of interest. Current density (with pulse duration at 1ms and frequency 2Hz) of around 1 mA for superficial nerves and 1.5-2mA for deeper nerves is enough to elicit a desired motor response(5). Eliciting a motor response at an even higher current density can be discomforting to the patient as well as misleading to the operator as neural structures can get stimulated through tissues and fascial planes (6). Similarly, Current density can also be used to predict the intra-fascicular or intraneural needle placement. Bigeleisen et al showed that minimum stimulation (Median [interquartile range]) threshold outside was 0.60 mA [0.40-1.0] and inside 0.30 mA [0.20-0.40], where, the difference of 0.30 mA was statistically significant (7). Therefore, a lower limit for the current density can be used as a safety margin beyond which no muscle activity should be elicited by using PNS.

So, considering the additional benefits of PNS Guidance that it can potentially concur in facilitating UGRA in achieving effective and safer PNB, we propose and design a randomized

control trial by comparing the UGRA with and without PNS Guidance in achieving PNB and its outcomes.

OBJECTIVES

Primary Objective of this study is to compare the success rate of Ultrasound guided Supraclavicular brachial plexus block with and without PNS guidance.

Secondary objectives are frequency of needle re-adjustments with US + PNS guidance depending upon the added information obtained via the PNS, duration of PNB procedure, rate of complications such as nerve damage between the two group, intra-op rescue analgesic requirement and conversion to General Anaesthesia.

Primary Outcome:

Time to onset of nerve blockade and rate of success of blockade between the study groups.

Secondary Outcome:

Needle re-adjustments, duration of PNB procedure, rate of complications, intra-op rescue analgesic requirement and conversion to General Anaesthesia between the study groups.

RISKS AND BENEFITS OF STUDY:

Benefits of the study are that we will be able to identify the most suitable modality for performing the PNB in terms of rate of success, time to onset of block and rate of complications, allowing patients to receive much effective and safe PNB.

Risks of this study include infection, vascular puncture, hematoma, nerve damage, temporary phrenic nerve blockade, Horner's syndrome, laryngeal nerve blockade and Local Anaesthetic Systemic Toxicity.

OPERATIONAL DEFINITION

Pain Score: Pain Scoring on a 0 to 10 numerical rating scale where 0 would be no pain and 10 would be the worst possible pain experienced.

Bradycardia: Heart Rate of less than 60bpm.

Hypotension: Mean Arterial Pressure of less than 65mmHg.

Significant rise in Blood Pressure: Sudden rise of more than 20% in systolic blood pressure from the baseline.

Significant rise in Heart Rate: Sudden rise of more than 20% in Heart Rate from the base line.

Successful Block: Patients showing complete sensory and motor blockade in the distribution of blocked nerves after 25mins of PNB.

Partially Successful Block: Patients showing in-complete or patchy sensory and motor blockade in the distribution of blocked nerves after 25mins of PNB.

Failed Block: Patients showing absolutely no loss of sensory and motor blockade in the distribution of blocked nerves after 25mins of PNB.

HYPOTHESIS

'Addition of PNS Guidance to UGRA will increase the success rate of PNB'.

MATERIAL AND METHODS

Study design:
Single Blinded, Randomized Controlled Trial.

Setting:
The Aga Khan University Hospital, Karachi

Duration of study:
2 Years

Sample size:
An anticipated sample size of minimum 44 patients will need to be included in this study with 99% confidence interval and 95% power, of which, 22 should receive receive PNB solely under the Ultrasound Guidance and 22 should receive PNB under the Ultrasound Guidance supplemented with PNS. Sample has been calculated by using OpenEpi software's 'Sample size for comparing two means' function. Where, a mean (standard deviation) time (minutes) to onset of sensory blockade for patients who received PNB under US guidance was inserted as 10 (2.4506), while for patients who received received PNB under the Ultrasound plus PNS guidance was inserted as 7.5 (1.2253). The ratio of between both the groups was 1. These estimates were taken from the study conducted by Gökhan Demirelli et al, where they assessed ultrasound and ultrasound plus nerve stimulator guided Median Nerve Blockade as part of axillary plexus block (3). The study originally reported the onset of sensory blockade times in median (IQR), which were then converted to Mean (standard deviation) for the purpose of sample size calculation based upon the sample from Luo et al. (8) and Wan et al. (9).

Sampling technique

Non-probability consecutive sampling with randomized group allocation.

Sample selection

Inclusion criteria:

- Aged 18 years and older.
- ASA 1 to IV
- No contraindications to regional anaesthesia.
- Operative site at mid to lower arm, elbow, forearm, wrist, and hand.
- Ability to provide informed consent and reliably report symptoms to the research team for regional anesthesia.

Exclusion criteria:

- Patient's refusal to participate.
- Inability to provide first-party consent due to cognitive impairment.
- Cognitive dysfunction which can lead to difficulties in communication and cooperation of patient.
- Preexisting neuropathy.
- Preexisting coagulopathy.
- Patients who will be shifted to ICU due to post - operative ventilatory support.

Randomization:

Patients will be randomly divided by block randomization into two study groups at a ratio of 1:1 using a computer-generated random number.

Blinding:

Study will be single blinded where only the patients will be unaware of the study group they will be made part of.

Funding

Investigators, after getting approval from ARC and ERC, will request for departmental grant for funding their research so study related interventions and consumables will not be charged to the patient. Insurance cover for the management of potential study related adverse events will be provided by research grant fund.

Study groups

Group US: Patients in this group will receive PNB solely under the Ultrasound Guidance.

Group US+PNS: Patients in this group will receive PNB under the Ultrasound Guidance supplemented with PNS.

Data collection

Patients' enrollment in the study will begin after obtaining approval from the ERC and Clinical Trials unit. The trial will be conducted in compliance with Good Clinical Practice (GCP). Operating Room lists will be reviewed a day before and patients planed for surgeries involving regions of mid to lower arm, elbow, forearm, wrist, and hand will be considered for inclusion in study. These patients will then be interviewed in the ward or day care unit after they get admitted for surgery, where they will be assessed for participation in study based upon the inclusion and exclusion criteria. Patients fulfilling such criteria will be considered for participation and their primary surgeon will be informed of such. Patients, whose surgeon agrees for their participation, will be handed over the consent form after explaining them the whole procedure, advantages, and disadvantages of the procedure and their absolute free will to be part of the study. Patients who will consent to be part of our trial will be enrolled in our study. Study participants will then be taken to the OR where they will be applied with standard monitoring including Non-invasive Blood Pressure monitoring, Electrocardiography and Pulse Oximetry, and supplemental oxygen will be applied to the patients via nasal cannula at 4L/min. An intravenous access of 20 or 22 gauge will be established in contralateral arm for background fluid infusion and emergency intravenous access. Participants will then be positioned supine with slight head rotation to the contralateral side. PNB will be performed by a consultant anaesthetist proficient in performing supraclavicular block. In the US group, Ultrasound linear probe will be applied in the supraclavicular fossa in sterile manner and will be positioned to obtain short axis view of subclavian artery and first rib to achieve satisfactory image of elliptical hypoechoic trunks and divisions of brachial plexus at the supraclavicular fossa. 1–2 mL of 2% lignocaine will be injected subcutaneously into the skin 1 cm lateral to the transducer by using 27-gauge needle to decrease discomfort during block needle insertion The block needle will be introduced in lateral to medial direction under the US Guidance in-plane to the probe. Needle will then be directed towards the junction of first rib and subclavian artery, aiming for the neural cluster of brachial plexus. Once the operator feels satisfied with the needle tip placement, a negative aspiration will be attempted to rule out in-advert intravascular puncture and then 25ml of 0.5% Bupivacaine Local Anaesthetic (LA) will be injected all around the said neural cluster while observing for the hydro-dissection and spread of Bupivacaine all around the neural cluster. Needle will be redirected if desired spread of LA does not occur around the neural cluster until such is achieved with LA injection. In the US + PNS group, majority of the procedure similar to what was performed in the US group will be followed with differences that an insulated PNS compatible block needle will be used to perform the PNB and once the operator will be satisfied of their needle placement, a current of 1.0 mA will be delivered via block needle to achieve desired muscle response i.e., motor response in arm, forearm and/or hand. Failure to get such response will prompt the operator to re-adjust the block needle until such is achieved. Once desired muscle response will be achieved, current of PNS will be gradually decreased to up till 0.4 mA, where no muscle response should be elicited. Presence of muscle response at 0.4 mA will suggest intraneural placement of block needle and operator will re-adjust the needle until such is abolished while preserving muscle response for the current window between 0.5-1.0 mA.

Afterwards, progression of sensory blockade will be assessed by evaluating for absence of sensation to cold using an ice pack in musculocutaneous, median, ulnar, and radial nerve distribution and comparing it with contralateral arm. This assessment will be done every 1 minute after completion of injection until complete sensory blockade in each of the four major nerve territories. Time to onset of sensory blockade will be defined as the time duration from injection completion to sensory blockade in any of the four nerve territories. Whereas time to complete sensory blockade will be defined as the time duration from injection completion to sensory blockade in all the four nerve territories. Progression of motor blockade will be assessed by asking the patient to move their elbow, wrist and fingers and observing for absence of movement (plegia). This assessment will be done every 2 minutes after completion of injection until complete motor blockade is achieved. Time to onset of motor blockade will be defined as the time duration from injection completion to plegia at either elbow, wrist, or fingers. Whereas time to complete motor blockade will be defined as the time duration from injection completion to plegia at elbow, wrist, and fingers. Once complete motor and sensory blockade will be achieved, surgeon will be given go-ahead to proceed with surgery. Any intra-op analgesic requirement will be documented. After completion of surgery, patients will be shifted to PACU where their surgical pain will be assessed. Patients will be followed for any PNB related complication.

ETHICAL CONSIDERATION:

The information provided will remain confidential. Nobody except the principal investigator will have access to it. Name and identity will also not be recorded at any time and all the important details by which identity can be revealed will not be mentioned on the Proforma. However, the data may be seen by Ethical Review Committee and may be published in Journals and somewhere.

DATA ANALYSIS

The data of the study will be encoded and analyzed through SPSS. The overall quantitative variables such age, weight, height, duration of PNB, duration of onset of nerve blockade, etc. will be conveyed as mean ± SD or median (IQR) depending upon their distribution. While, for the qualitative variables such as gender, co-morbidities, needle re-adjustment, success of block etc., frequency and percentages will be used. Stratification analysis will be done with respect to US guided and US + PNS guided PNB groups to fulfill primary and secondary outcomes such as time to onset of nerve blockade, success of block, needle re-adjustments, duration of PNB procedure, rate of complications, intra-op rescue analgesic requirement and conversion to general anaesthesia. Furthermore, the association between US guided and US + PNS guided PNB groups with respect to outcome variables will be evaluated by independent t-test or Mann Whitteny U test and Chi-square test of association. p value of < 0.05 will be considered as statistically significant.

DATA HANDLING

The primary investigator will be responsible for data handling. The primary investigator will be responsible for monitoring the study for protocol compliance, ethical standards, regulatory

compliance and data quality. The confidentiality of the participants will be maintained by assigning each patients a number. All Hardcopies of the data will be stored under lock and key, While, all soft copies will be password protected. A per regulatory requirements this data will be encrypted and stored for 15 years.

ADVERSE EVENTS

Adverse Events are defined as 'Any untoward medical occurrence in a trial patient to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure.

Such events include, infection, vascular puncture, hematoma, nerve damage, temporary phrenic nerve blockade, Horner's syndrome, and laryngeal nerve blockade.

Patient will be followed and monitored till the resolution of symptoms and discharge. all AEs will be reported to the ERC in the progress report.

SERIOUS ADVERSE EVENTS

Serious Adverse Events are defined as an untoward event that: Results in death; Is life-threatening; Requires hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability or incapacity; Or is otherwise considered medically significant by the Investigator.

The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Patients must be formally admitted – waiting in out-patients or A&E does not constitute an SAE (even though this can sometimes be overnight). Similarly, planned hospitalizations that clearly are not related to the condition under investigation or hospitalizations/prolongation of hospitalization due to social reasons should not be considered as SAEs. Such serious adverse events can include pneumothorax, intravascular injection of local anaesthetic and local anaesthetic systemic toxicity.

All SAEs will be reported within 24 hours to the sponsor, ERC, and hospital management through online incident report.

Insurance cover for the management of potential adverse events associated with the intervention will be taken before initiating the study.

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