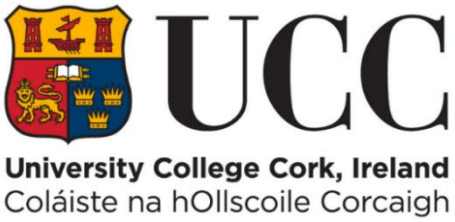
Ollscoil na hÉireann, Corcaigh

National University of Ireland, Cork



Pharmacological Optimisation of Ultrasound Guided Axillary Brachial Plexus Block

Thesis presented by

Anil Kumar Malladihalli Ranganath

MBBS, DA, FCAI, EDRA, DPMCAI

for the degree of

Doctor of Medicine

University College Cork
Department of Anaesthesia, Intensive Care and Pain Medicine,
Cork University Hospital

Head of Department: Professor Paul Redmond

Supervisors

Dr Gabriella Iohom, PhD

Professor George Shorten, PhD

Submitted July 2021

Table of contents

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

_____

Anil Kumar Malladihalli Ranganath

Acknowledgement

First, I would like to express my sincere gratitude to my supervisors Dr Gabriella Iohom and Professor George Shorten for their encouragement, continuous support, and patience during my thesis work. I would like to extend my sincere thanks to Dr Gabriella Iohom in particular for her assistance at every stage of the research work.

I would also like to thank the department of anaesthesia, CUH, for giving me an opportunity to participate in research activities during my fellowship in regional anaesthesia. I wish to thank Dr Brian O'Donnell for imparting the vast practical knowledge and expertise in the field of regional anaesthesia.

The work included in this thesis would not have been possible without the support and collaboration of my co-authors and fellow research colleagues Karthik, Jasim, Osman, Tomas, and Michael.

Finally, my sincere thanks to my family for their continuous and unparalleled love and support, to whom this entire work is dedicated. I am forever grateful to my parents for giving me the opportunities and experiences that have made me who I am. I would like to acknowledge the support and encouragement of my wife, Priyanka and my kids, Gagan and Diya during the many hours spent writing this thesis.

Publications arising from or associated with this work

1. Ranganath A, Srinivasan KK, Iohom G. Ultrasound guided axillary brachial plexus block. *Med Ultrason* 2014;16: 246-51.
2. Ranganath A, Rauf J, Srinivasa KK, Iohom G. Effect of two volumes (10 and 30 mL) of lidocaine 2% plus epinephrine on the duration of axillary brachial plexus block. A randomised controlled trial. *European journal of anaesthesiology.* 2022;39(1):84-87
3. Ranganath A, Ahmed O, Iohom G. Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled trial. *Med Ultrason.* 2021.
4. Ranganath A, Hitka T, Iohom G. Effects of clonidine as adjuvant to lidocaine with epinephrine in ultrasound guided axillary brachial plexus block: a randomised controlled trial. *Journal of clinical medicine.* 2021;10(18).
5. Ranganath A, Rauf J, Srinivasa KK, Iohom G. Effect of two volumes (10 and 30 mL) of lidocaine 2% plus epinephrine on the duration of axillary brachial plexus block. A randomised controlled trial. *Anaesthesia & Analgesia, Volume 133, Supplement 2, 3S, 1-5 September 2021.* **Abstract**
6. Ranganath A, Ahmed O, Iohom G. Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled trial. *Anaesthesia & Analgesia, Volume 133, Supplement 2, 3S, 1-5 September 2021.* **Abstract**
7. Ranganath A, Hitka T, Iohom G. Effects of clonidine as an adjuvant to lidocaine with epinephrine in ultrasound guided axillary brachial plexus block: a randomised controlled trial. *Anaesthesia & Analgesia, Volume 133, Supplement 2, 3S, 1-5 September 2021.* **Abstract**

Abstract presentations arising from or associated with this work

1. 17th World Congress of Anaesthesiologists 2021, WFSA

   Ranganath A, Rauf J, Srinivasa KK, Iohom G. Effect of two volumes (10 and 30 mL) of lidocaine 2% plus epinephrine on the duration of axillary brachial plexus block. A randomised controlled trial. **Poster presentation**.

2. 17th World Congress of Anaesthesiologists 2021, WFSA

   Ranganath A, Ahmed O, Iohom G. Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled trial. **Poster presentation.**

3. 17th World Congress of Anaesthesiologists 2021, WFSA

   Ranganath A, Hitka T, Iohom G. Effects of clonidine as adjuvant to lidocaine with epinephrine in ultrasound guided axillary brachial plexus block: a randomised controlled trial. **Poster presentation.**

Chapter 1

Introduction and Objectives

1.1 Introduction

Peripheral nerve blocks provide significant advantages in the perioperative care of the patient undergoing surgery, including improved postoperative analgesia, a reduction in adverse events, shorter recovery time, and expedited hospital discharge when compared to general anaesthesia.[1,2]

Safe performance of brachial plexus block warrants consideration of several factors, such as i. an understanding of relevant anatomy, ii. effectiveness and potential adverse effects of brachial plexus approach for the intended site of surgery, iii. methods of nerve localisation, and iv. selection of pharmacological agents to enhance the quality of block.

Interscalene block provides surgical anaesthesia for shoulder and proximal humerus, whereas a supraclavicular approach provides the most widespread surgical anaesthesia for the whole arm. The infraclavicular approach provides surgical anaesthesia similar to axillary approach covering elbow, forearm, and hand. The axillary approach to brachial plexus block is considered the safest and most commonly performed of the four approaches[3] because of its superficial anatomical configuration, ease of performance and favourable safety profile. The risk of phrenic nerve block and pneumothorax are not features of axillary block, while they can complicate interscalene, supraclavicular, and infraclavicular approaches. Inadvertent intravascular and intraneural injections with resultant local anaesthetic systemic toxicity and nerve injury are the predominant significant risks.

Methods of nerve localisation have evolved and been refined from earlier paraesthesia and perivascular or transarterial techniques to peripheral nerve

stimulation. With the emergence of ultrasound-guidance, regional anaesthesia has been revolutionised and currently, an ever-growing amount of evidence is supportive of its use. Ultrasound use has been shown to improve the quality of peripheral nerve block by hastening block onset and enhancing block success rates. Ultrasound has also improved nerve block safety by facilitating successful nerve block with comparatively small doses of local anaesthetic when compared to alternate techniques,[4-6] thereby mitigating against the occurrence of local anaesthetic systemic toxicity.

The choice of local anaesthetics in peripheral nerve block is dependent upon variables such as the desired onset and duration of motor and sensory nerve block, the expected duration of surgery and the requirement for post-surgical regional analgesia. Evidence to support the superiority of one over another is limited. The intermediate acting agent, Lidocaine demonstrates desirable onset characteristics when compared to longer acting local anaesthetics, which may be desirable for rapid turnover in an ambulatory surgery.

Other factors that can modify the effectiveness of peripheral nerve blockade are the volume and concentration (and dose) of local anaesthetic injected. In the past, there has been a propensity to use a higher volume of local anaesthetic to achieve successful peripheral nerve blocks.[7,8] Recent studies have shown that similar efficacy can be achieved with lesser volumes.[9] Given the potential benefit of limiting the volume in reducing adverse events, it is uncertain whether use of comparatively small doses of local anaesthetic adversely influences nerve block characteristics. Previously, studies examining this area have produced inconsistent results.[10-13] Similarly, local anaesthetic volume and concentration influences block efficacy;

however, block efficacy, onset time, and duration of peripheral nerve block for a given injectate composition is not precisely predicatble.[14-19]

Ultrasound-guided techniques of peripheral nerve block have become the gold standard with improvements in efficacy, ease of performance and safety. The potential benefit of perioperative regional anaesthesia should extend beyond acute pain relief. Various adjuvants have been combined with local anaesthetic to prolong the duration and enhance the quality of blocks. Epinephrine is most widely used adjunct to local anaesthetics to prolong the duration of lipophobic local anaesthetic such as lidocaine by vasoconstriction. It also acts as a marker to detect inadvertent intravascular injection and potentially limits the local anaesthetic systemic toxicity.[20] Clonidine, a selective α_2 adrenoreceptor with a weak α_1 activity when combined with local anaesthetics in peripheral nerve block has shown to improve the quality of block and prolong the duration of anaesthesia and analgesia. Doses as great as 150 µg have been administered with minimal side effects.[21] It has been proposed that clonidine exerts its effect by influencing resorption of local anaesthetics through local vasoconstriction[22] or it may have a direct action on the nerve fiber.[23]

The advent of ultrasound guidance has enabled more accurate placement of local anaesthetic paraneurally. This opens up a new possibility to precisely study the effect of local anaesthetic volumes, volume/concentration ratio (dose) and adjuvants on the characteristics of the nerve block. We used lidocaine with epinephrine, which is the most commonly used agent in our institution, as the primary local anaesthetic agent for a number of reasons. Firstly, it produces rapid block onset. This is especially relevant when regional anaesthesia is used as for surgical anaesthesia. Secondly, it has a better safety profile than other amide local anaesthetics such as bupivacaine or

ropivacaine in the context of local anaesthetic toxicity. Clonidine was chosen as it has been shown to be beneficial as an additive although the combination with epinephrine has not been studied before. To this end, we designed a series of studies with specific aims.

1.2 Objectives

The overall objective of this research is to evaluate i. the effect of administering local anaesthetic at various dose, volume, and concentration, and ii. addition of adjuvants to local anaesthetic solution, on the clinical characteristics and efficacy of ultrasound guided axillary plexus block for the peri-operative management of patients undergoing upper limb trauma surgery.

The specific aims relating to the studies included in this thesis are:

Study 1 (Chapter 2) : To evaluate the duration of sensory and motor block in patients undergoing ultrasound guided axillary brachial plexus block using 10 and 30 ml of 2% lidocaine with 1:200,000 epinephrine.

Study 2 (Chapter 3) : To evaluate the onset of sensory and motor block in patients undergoing ultrasound guided axillary brachial plexus block using 400mg of lidocaine with epinephrine administered as either 20ml of 2% lignocaine with adrenaline or 40ml of 1% lignocaine with epinephrine.

Study 3 (Chapter 4) : To evaluate the onset and duration of sensory and motor block in patients undergoing ultrasound guided axillary brachial plexus block using 20ml 2% lidocaine with 1:200,000 epinephrine with or without clonidine 1 µg/kg.

1.3 References for chapter 1

1. Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. *Anesthesia and Analgesia.* 2005;101(6):1634-1642.
2. Hadzic A, Williams BA, Karaca PE, et al. For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. *Anesthesiology.* 2005;102(5):1001-1007.
3. Klein SM, Pietrobon R, Nielsen KC, Warner DS, Greengrass RA, Steele SM. Peripheral nerve blockade with long-acting local anesthetics: a survey of the Society for Ambulatory Anesthesia. *Anesthesia and Analgesia.* 2002;94(1):71-76, table of contents.
4. Choi S, McCartney CJ. Evidence Base for the Use of Ultrasound for Upper Extremity Blocks: 2014 Update. *Regional Anesthesia and Pain Medicine.* 2016;41(2):242-250.
5. Neal JM, Brull R, Horn JL, et al. The Second American Society of Regional Anesthesia and Pain Medicine Evidence-Based Medicine Assessment of Ultrasound-Guided Regional Anesthesia: Executive Summary. *Regional Anesthesia and Pain Medicine.* 2016;41(2):181-194.
6. Abrahams MS, Aziz MF, Fu RF, Horn JL. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. *British Journal of Anaesthesia.* 2009;102(3):408-417.
7. Koscielniak-Nielsen ZJ, Hesselbjerg L, Fejlberg V. Comparison of transarterial and multiple nerve stimulation techniques for an initial axillary

block by 45 mL of mepivacaine 1% with adrenaline. *Acta Anaesthesiologica Scandinavica.* 1998;42(5):570-575.

8. Chan VW, Perlas A, McCartney CJ, Brull R, Xu D, Abbas S. Ultrasound guidance improves success rate of axillary brachial plexus block. *Canadian Journal of Anaesthesia=Journal Canadien d'anesthesie.* 2007;54(3):176-182.
9. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. *Anesthesiology.* 2009;111(1):25-29.
10. Serradell A, Herrero R, Villanueva JA, Santos JA, Moncho JM, Masdeu J. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. *British Journal of Anaesthesia.* 2003;91(4):519-524.
11. 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(4):549-556.
12. Ponrouch M, Bouic N, Bringuier S, et al. Estimation and pharmacodynamic consequences of the minimum effective anesthetic volumes for median and ulnar nerve blocks: a randomized, double-blind, controlled comparison between ultrasound and nerve stimulation guidance. *Anesthesia and Analgesia.* 2010;111(4):1059-1064.
13. Schoenmakers KP, Wegener JT, Stienstra R. Effect of local anesthetic volume (15 vs 40 mL) on the duration of ultrasound-guided single shot axillary brachial plexus block: a prospective randomized, observer-blinded trial. *Regional Anesthesia and Pain Medicine.* 2012;37(3):242-247.

14. Taboada Muñiz M, Rodríguez J, Bermúdez M, et al. Low volume and high concentration of local anesthetic is more efficacious than high volume and low concentration in Labat's sciatic nerve block: a prospective, randomized comparison. *Anesthesia and Analgesia.* 2008;107(6):2085-2088.

15. Cappelleri G, Ambrosoli AL, Turconi S, Gemma M, Ricci EB, Cornaggia G. Effect of local anesthetic dilution on the onset time and duration of double-injection sciatic nerve block: a prospective, randomized, blinded evaluation. *Anesthesia and Analgesia.* 2014;119(2):489-493.

16. Bertini L, Palmisani S, Mancini S, Martini O, Ioculano R, Arcioni R. Does local anesthetic dilution influence the clinical effectiveness of multiple-injection axillary brachial plexus block?: a prospective, double-blind, randomized clinical trial in patients undergoing upper limb surgery. *Regional Anesthesia and Pain Medicine.* 2009;34(5):408-413.

17. Krenn H, Deusch E, Balogh B, et al. Increasing the injection volume by dilution improves the onset of motor blockade, but not sensory blockade of ropivacaine for brachial plexus block. *European Journal of Anaesthesiology.* 2003;20(1):21-25.

18. Fredrickson MJ, Smith KR, Wong AC. Importance of volume and concentration for ropivacaine interscalene block in preventing recovery room pain and minimizing motor block after shoulder surgery. *Anesthesiology.* 2010;112(6):1374-1381.

19. González AP, Bernucci F, Techasuk W, Pham K, Finlayson RJ, Tran DQ. A randomized comparison between 3 combinations of volume and concentration of lidocaine for ultrasound-guided infraclavicular block. *Regional Anesthesia and Pain Medicine.* 2013;38(3):206-211.

20. Neal JM, Gerancher JC, Hebl JR, et al. Upper extremity regional anesthesia: essentials of our current understanding, 2008. *Regional Anesthesia and Pain Medicine.* 2009;34(2):134-170.

21. McCartney CJ, Duggan E, Apatu E. Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Regional Anesthesia and Pain Medicine.* 2007;32(4):330-338.

22. Hutschala D, Mascher H, Schmetterer L, et al. Clonidine added to bupivacaine enhances and prolongs analgesia after brachial plexus block via a local mechanism in healthy volunteers. *European Journal of Anaesthesiology.* 2004;21(3):198-204.

23. Kroin JS, Buvanendran A, Beck DR, Topic JE, Watts DE, Tuman KJ. Clonidine prolongation of lidocaine analgesia after sciatic nerve block in rats Is mediated via the hyperpolarization-activated cation current, not by alpha-adrenoreceptors. *Anesthesiology.* 2004;101(2):488-494.

Chapter 2

Review article :

Ultrasound guided axillary brachial plexus block.

2.1 Abstract

The axillary brachial plexus block is an effective and widely used technique for providing surgical anaesthesia at and below the elbow. Safe performance of the block requires thorough knowledge of relevant anatomy and understanding of the technique. Methods of axillary brachial plexus block are briefly reviewed with particular reference to ultrasound guidance.

Keywords: axillary brachial plexus block, regional anaesthesia, ultrasound

2.2 Introduction

Peripheral nerve blocks have seen a big resurgence of interest in the past decade especially with the advent of ultrasound. Nerve blocks have evolved from being an art that only a few physicians can master to a more objective and transferable skill largely due to the introduction of ultrasound guidance. Peripheral nerve blocks today are a major component of perioperative multimodal analgesia.[1,2] In particular, for upper extremity surgeries, brachial plexus blocks (interscalene, supraclavicular, infraclavicular and axillary approaches) have been consistently shown to be associated with time-efficient anaesthesia, faster recovery, fewer adverse events, better analgesia, and greater patient acceptance when compared to general anaesthesia.[3-5]

The axillary brachial plexus block (ABPB) provides surgical anaesthesia at and below the elbow. The technique is relatively easy to perform because of the superficial location of the plexus and relatively small risk of complications when compared to interscalene (e.g., phrenic nerve block, spinal cord injury, or vertebral artery puncture) or supraclavicular (e.g., pneumothorax) approaches.[6] Inadvertent intraneural and intravascular injections are the only significant risks. Various methods of ABPB have been described such as paraesthesia-seeking, nerve-stimulating, perivascular, trans-arterial, and ultrasound-guided techniques. This review will focus on the ultrasound guided axillary brachial plexus block.

2.3 Anatomy

The brachial plexus is derived from the ventral rami of C5-8 and T1 nerve roots in most individuals. Occasionally contributions from C4 and T2 nerve roots create a 'prefixed' or 'postfixed' plexus.[7] The roots emerge from the intervertebral foramina and continue between scalenus anterior and medius muscles. Here roots unite to form trunks (upper, middle, and lower) and pass downward over the posterior triangle of the neck and the first rib. At the lateral border of the first rib, behind the clavicle, each trunk divides into divisions (anterior and posterior). These divisions continue into the axilla and form the cords. The anterior divisions of the upper and middle trunks unite to form the lateral cord, while the anterior division of the lower trunk continues as the medial cord. All three posterior divisions unite to form the posterior cord. These cords are named according to their position around the axillary artery. Each cord ends near the lower border of the pectoralis minor muscle by dividing into two terminal branches. The lateral cord gives off the lateral branch of median nerve and terminates as musculocutaneous nerve. The medial cord gives off the medial branch of the median nerve and terminates as the ulnar nerve. The posterior cord gives off the axillary nerve and terminates as the radial nerve. All these terminal nerves along with the medial cutaneous nerve of arm, forearm and intercostobrachial nerve provide the sensory and motor supply of the upper extremity. The cords, the terminal branches and the vessels lie within an incomplete fascial sheath derived from the prevertebral fascial layer.[8]

At the level of axilla, the median, ulnar and radial nerves lie within the neurovascular bundle. The musculocutaneous nerve lies outside the sheath in the plane between the biceps and coracobrachialis muscle, as it leaves the lateral cord before the cords

enter the axilla. Within the fascia, in relation to the axillary artery, the nerves are arranged as follows: (1) median-lateral and anterior, (2) ulnar-medial and anterior, and (3) radial-medial and posterior. The musculocutaneous nerve appears lateral and posterior to the artery.

2.4 Principles of brachial plexus block

The brachial plexus can be blocked at its various anatomical divisions from nerve roots to its individual terminal branches. The choice of approach depends upon the sensory and motor innervations of the surgical site. The interscalene approach blocks the plexus at the level of roots, thus it is used for shoulder and proximal humerus procedures. The supraclavicular approach blocks the plexus at the level of trunks and divisions providing the most widespread surgical anaesthesia for the whole arm. The infraclavicular approach blocks the cords, whereas the axillary approach blocks the terminal branches thus providing surgical anaesthesia for the elbow, forearm, and hand. In addition, the axillary block also provides cutaneous anaesthesia for the inner upper arm which is suitable for procedures requiring tourniquet. Overall, the axillary approach is considered the safest approach because of the lowest risk of serious complications.

2.5 Ultrasound guided axillary brachial plexus block

Abramowitz and Cohen described in 1981 the use of Doppler ultrasound to identify the axillary artery, an essential landmark during a difficult perform ABPB.[9] It was, however, the use of B-mode ultrasound in 1989 for axillary block performance that paved the way for ultrasound-guided peripheral nerve blocks.[10] Ultrasound guidance is ideally suited for ABPB for a variety of reasons. The nerves are superficial and therefore easier to identify. The shallow depth of the nerve means that the needle for in-plane approach will be almost perpendicular to the direction of the ultrasound beam, thereby greatly improving needle visibility, which in turn will allow for accurate needle positioning with minimal needle redirections. The vast anatomical variations in position of vascular and neural structures relevant to axillary block[11] will make ultrasound even more suited when compared to conventional landmark guided approach. As one would expect, ultrasound guidance has been shown to reduce block performance time, improve block success rate,[12-14] shorten onset time,[15,16] reduce vascular puncture[17,18] and achieve a reduction in the volume of local anaesthetic required.[19]

Ultrasound anatomy

The patient is made comfortable in supine position with the arm abducted and the elbow flexed to 90 degrees. After skin and probe preparation, a linear 38-mm, high frequency 10-12 MHz transducer is placed in the transverse plane at the lateral border of pectoralis major muscle to obtain the best view of the brachial plexus. Image quality is optimised with selection of appropriate depth (within 1-2 cm), focus range (within 1cm) and gain. The structures of interest are very superficial with the pulsating axillary artery localised within 1 cm (fig 1). Easing the pressure on the

transducer often reveals one or more axillary veins, often located medially to the artery (fig 2, fig 3). Surrounding the axillary artery, one will find the three out of four terminal branches of the brachial plexus: the median (superficial and lateral to the artery), the ulnar (superficial and medial to the artery) and the radial (posterior and lateral or medial to the artery) nerves. They often have honeycomb appearance with heterogeneous echogenicity. The fourth terminal branch, the musculocutaneous nerve is often seen as a hyperechoic flattened oval shape nerve in the plane between the biceps and coracobrachialis muscles. There is a considerable variation in the position of the nerves among individuals. The median nerve is most commonly seen at 11-12 o'clock position, the ulnar nerve at 2-3 o'clock, the radial nerve at 4-6 o'clock and the musculocutaneous commonly seen at 8-9 at o'clock in relation to the artery.[20]

Moving the transducer proximally towards the axilla and distally towards the elbow allows appreciation of the course of each nerve. Of all the nerves, the radial nerve is often difficult to visualise and block. It is important to exclude the post cystic enhancement artefact beneath the artery. Identification of the confluence of the tendons of the latissimus dorsi and teres major with ultrasound may improve the chance of visualising the radial nerve (fig 4). It lies directly anterior to the humeral insertions of the tendons, with anatomic variation of this relation being quite uncommon.[21]

2.6 Technique

Needle insertion

In plane approach

A short-bevelled 5 cm 22G insulated needle is inserted parallel to the long axis of the transducer from the lateral side (fig 5). As the needle is in the same plane as the ultrasound beam, the path of the advancement can be visualised in real time as the needle approaches the target nerves (fig 6, fig 7). Ideally, the radial nerve should be targeted first, as it lies posterior to artery, in order to prevent displacing the structures of interest to deeper and obscuring the median and ulnar nerves. The musculocutaneous nerve should be blocked separately outside the neurovascular bundle.

Out of plane approach

The needle insertion is at the as the midpoint of the upper edge of the ultrasound probe (fig 8). Constant injection of small quantity of injectate is necessary in order to identify the position of the needle tip. In terms of safety, the in-plane approach offers better visualisation of the needle. Importantly, the routine of identifying the axillary veins using colour Doppler (fig 9) as they can be easily compressed with the transducer and visualising the injectate is paramount. Frequent aspiration, slow administration of 1-2 mL of local anaesthetic and visualisation of the spread of injectate around the nerve is critical to reduce the chance of intravascular or intraneural injection and to increase the chance of block success.

Choice and volume of local anaesthetic solution

This is determined by the desired duration of sensory analgesia. Lidocaine 1.5-2% with epinephrine 1:200000 or mepivacaine 1-1.5% provides effective blockade for 2.5-3 hours.[22,23] A longer duration may be achieved with use of ropivacaine 0.5% or levobupivacaine 0.5%.[24] Traditionally, greater volumes of local anaesthetic have been administered to achieve successful axillary brachial plexus block,[25,26] but recent studies have demonstrated that this can be achieved with even very low volumes of 2-4 mL lidocaine 1.5% per nerve[19] or ultra-low volume of 1 mL lidocaine 2% per nerve.[27] However, these volumes were believed to be operator dependent. It is recommended to use at least 4-5 mL of local anaesthetic solution for each nerve to achieve successful axillary brachial plexus block.

Perivascular vs perineural

Ultrasound guidance in the performance of axillary block can be applied to

i. perineural injection as described earlier, where the operator identifies and blocks the individual nerves, or
ii. perivascular technique, where the operator blocks the musculocutaneous nerve separately and deposits local anaesthetic solution around the axillary artery, which is in turn believed to achieve blockade of median, ulnar, and radial nerves.[28,29]

Both these techniques have been compared by Bernucci et al[30] and found to have similar success rates. However, the latter runs the risk of impaling nerves in inexperienced hands.

2.7 Conclusions

Axillary brachial plexus block is an effective and widely used technique for providing surgical anaesthesia at and below the elbow. It is relatively simple and safe when compared to the four approaches to brachial plexus. With the advent of ultrasound technology, there is a marked improvement in the success rate, shorter onset time and reduction in the volume required for successful block. Paramount importance should be given to continuous visualisation of the needle tip during forward advancement and the spread of injectate in order to minimise intravascular and intraneural injection.

2.8 Figures

Figure 1. Ultrasound scout scan of axilla showing AA: axillary artery, UN: ulnar nerve, RN: radial nerve, MCN: musculocutaneous nerve and CBM: coracobrachialis muscle

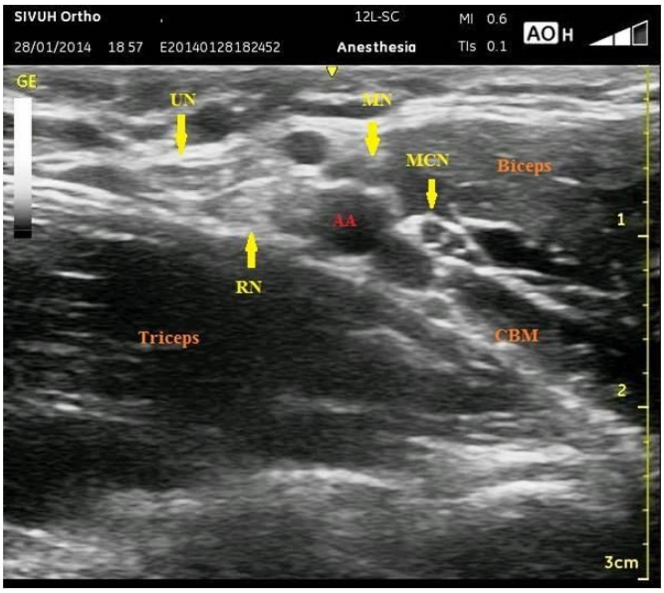


Figure 2. Ultrasound scout scan of axilla showing AV: axillary vein(s). UN: ulnar nerve, MN: median nerve, RN: radial nerve, AA: axillary artery

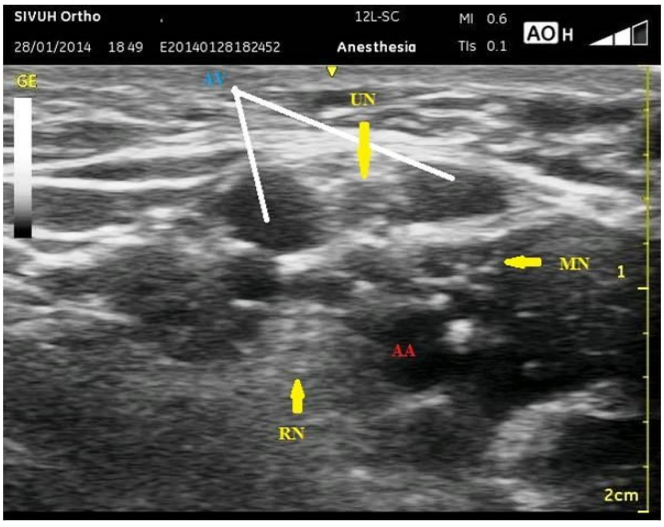


Figure 3. Axillary veins compressed by ultrasound probe

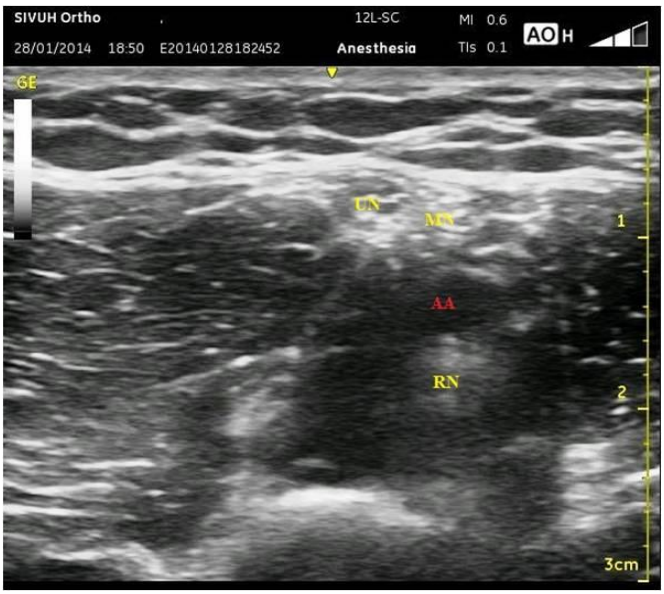


Figure 4. Arrow heads showing sonographic appearance of the conjoint tendon of the latissimus dorsi and teres major muscles

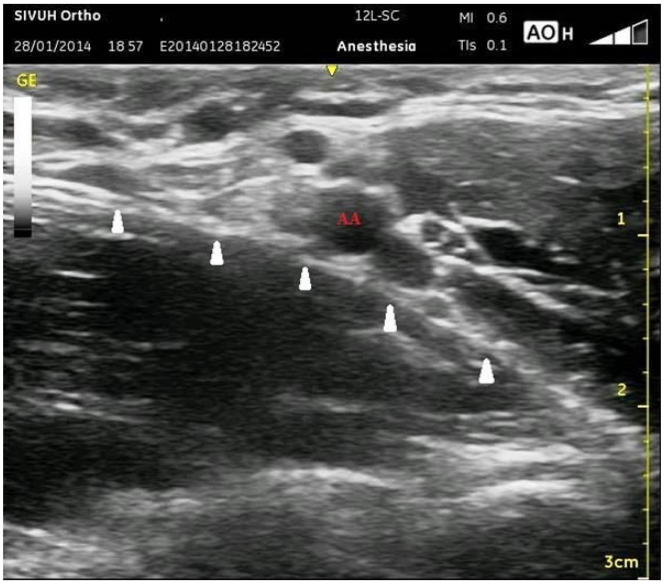


Figure 5. Ultrasound guided axillary brachial plexus block. In-plane approach of the needle with respect to probe. Also note the position of the patient's upper limb

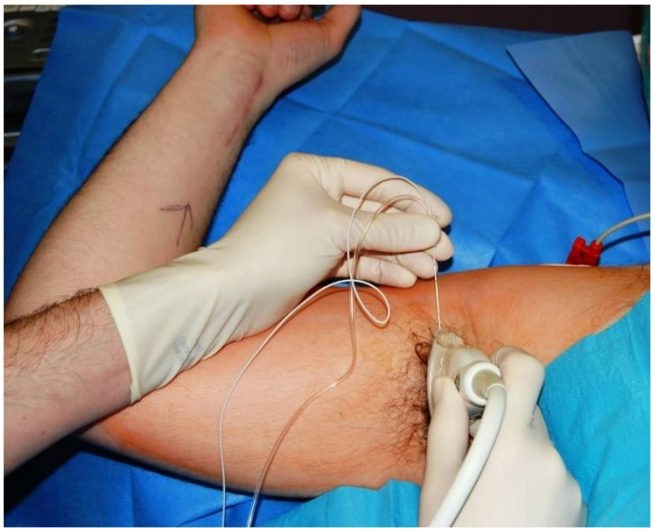


Figure 6. Needle trajectory and local anaesthetic spread around the ulnar nerve (shaded area)

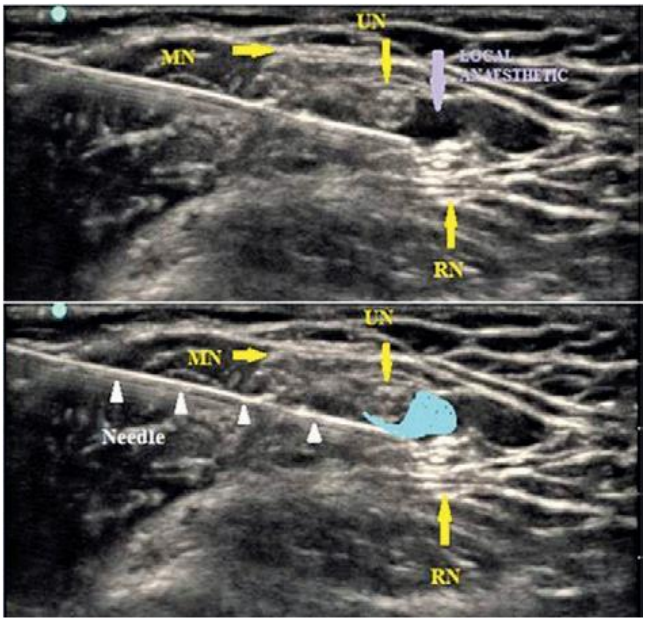
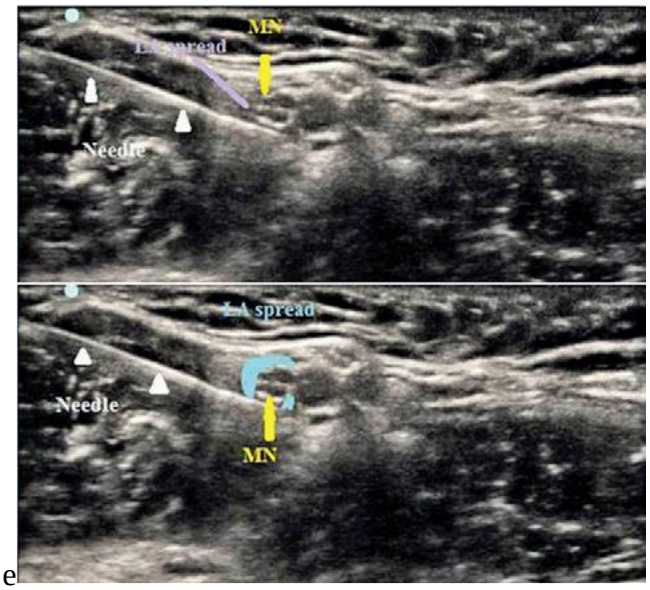


Figure 7. Needle trajectory and local anaesthetic spread around the median nerve (shaded area)



e

Figure 8. Ultrasound guided axillary brachial plexus block. Out-of-plane approach of the needle with respect to probe.

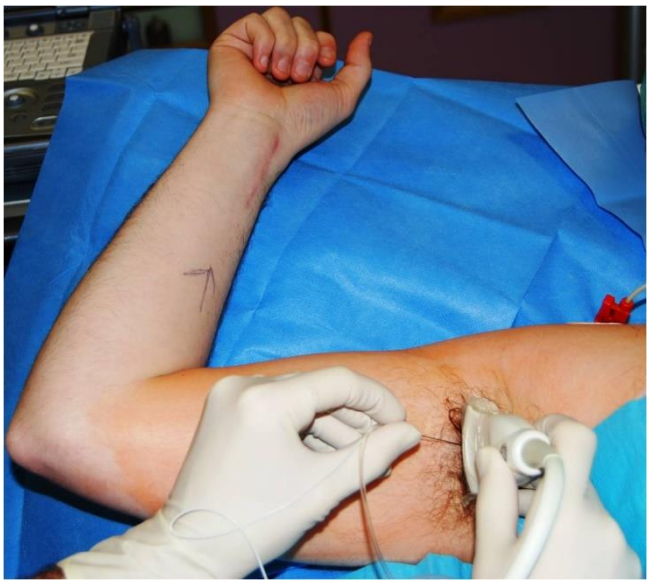
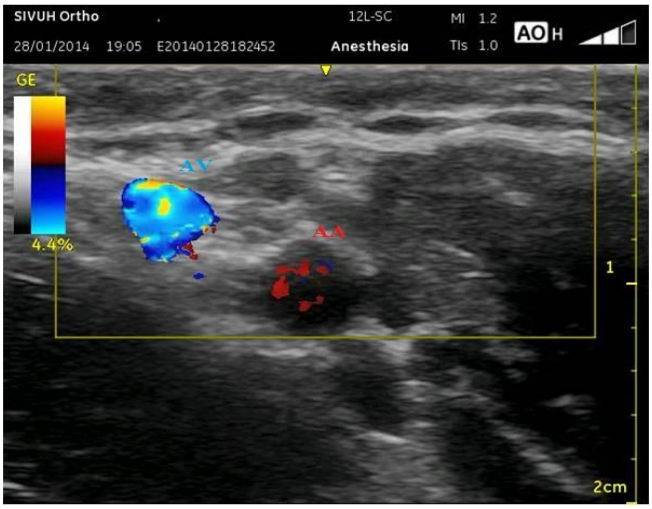


Figure 9. Doppler identification of vessels during ultrasound guided brachial plexus block.



2.9 References for chapter 2

1. Gritsenko K, Khelemsky Y, Kaye AD, Vadivelu N, Urman RD. Multimodal therapy in perioperative analgesia. Best Pract Res Clin Anaesthesiol 2014; 28: 59-79.
2. Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg 2005; 101: 1634-1642.
3. Hadzic A, Arliss J, Kerimoglu B, et al. A comparison of infraclavicular nerve block versus general anesthesia for hand and wrist day-case surgeries. Anesthesiology 2004;101: 127-132.
4. Lehmann LJ, Loosen G, Weiss C, Schmittner MD. Interscalene plexus block versus general anaesthesia for shoulder surgery: a randomized controlled study. Eur J Orthop Surg Traumatol 2015;25(2):255-261.
5. O'Donnell BD, Ryan H, O'Sullivan O, Iohom G. Ultrasound-guided axillary brachial plexus block with 20 millilitres local anesthetic mixture versus general anesthesia for upper limb trauma surgery: an observer-blinded, prospective, randomized, controlled trial. Anesth Analg 2009; 109:279-283.
6. Neal JM, Gerancher JC, Hebl JR, et al. Upper extremity regional anesthesia: essentials of our current understanding, 2008. *Regional anesthesia and pain medicine*. 2009;34(2):134-170.
7. Barash PG. Clinical Anesthesia. 6th ed. Lippincott Williams & Wilkins; 2009.
8. Barrett HD, Loughnane F, Finucane B, Shorten G. Peripheral nerve blocks and peri-operative pain relief. 1 ed. Philadelphia USA. Saunders; 2004.

9. Abramowitz HB, Cohen C. Use of Doppler for difficult axillary block. Anesthesiology 1981; 55: 603.

10. Ting PL, Sivagnanaratnam V. Ultrasonographic study of the spread of local anaesthetic during axillary brachial plexus block. Br J Anaesth 1989; 63: 326-329.

11. Ustuner E, Yilmaz A, Ozgencil E, Okten F, Turhan SC. Ultrasound anatomy of the brachial plexus nerves in the neurovascular bundle at the axilla in patients undergoing upper-extremity block anesthesia. Skeletal Radiol 2013;42: 707-713.

12. Chan VW, Perlas A, McCartney CJ, Brull R, Xu D, Abbas S. Ultrasound guidance improves success rate of axillary brachial plexus block. Can J Anaesth 2007; 54:176-182.

13. Williams SR, Chouinard P, Arcand G, et al. Ultrasound guidance speeds execution and improves the quality of supraclavicular block. Anesth Analg 2003;7:1518-1523.

14. Sites BD, Beach ML, Spence BC, et al. Ultrasound guidance improves the success rate of a perivascular axillary plexus block. Acta Anaesthesiol Scand 2006;50: 678- 684.

15. Kapral S, Greher M, Huber G, et al. Ultrasonographic guidance improves the success rate of interscalene brachial plexus blockade. Reg Anesth Pain Med 2008; 33: 253-258.

16. Marhofer P, Schrogendorfer K, Wallner T, Koinig H, Mayer N, Kapral S. Ultrasonographic guidance reduces the amount of local anesthetic for 3-in-1 blocks. Reg Anesth Pain Med 1998; 23: 584-588.

17. Yuan JM, Yang XH, Fu SK, et al. Ultrasound guidance for brachial plexus block decreases the incidence of complete hemi-diaphragmatic paresis or vascular punctures and improves success rate of brachial plexus nerve block compared with peripheral nerve stimulator in adults. Chin Med J (Engl) 2012; 125: 1811-1816.

18. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med 2013; 38: 289-297.

19. Harper GK, Stafford MA, Hill DA. Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound-guidance: a pilot study. Br J Anaesth 2010; 104: 633-636.

20. Christophe JL, Berthier F, Boillot A, et al. Assessment of topographic brachial plexus nerves variations at the axilla using ultrasonography. Br J Anaesth 2009; 103: 606-612

21. Gray AT. The conjoint tendon of the latissimus dorsi and teres major: an important landmark for ultrasound-guided axillary block. Reg Anesth Pain Med 2009; 34:179-180.

22. O'Donnell B, Riordan J, Ahmad I, Iohom G. Brief reports: a clinical evaluation of block characteristics using one milliliter 2% lidocaine in ultrasound-guided axillary brachial plexus block. *Anesthesia and analgesia.* 2010;111(3):808-810.

23. Marhofer P, Eichenberger U, Stockli S, et al. Ultrasonographic guided axillary plexus blocks with low volumes of local anaesthetics: a crossover volunteer study. *Anaesthesia.* 2010;65(3):266-271.

24. Gonzalez-Suarez S, Pacheco M, Roige J, Puig MM. Comparative study of ropivacaine 0.5% and levobupivacaine 0.33% in axillary brachial plexus block. Re Anesth Pain Med 2009; 34: 414-419.

25. Serradell A, Herrero R, Villanueva JA, Santos JA, Moncho JM, Masdeu J. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. Br J Anaesth 2003; 91: 519-524.

26. Vester-Andersen T, Husum B, Lindeburg T, Borrits L, Gothgen I. Perivascular axillary block IV: blockade following 40, 50 or 60 ml of mepivacaine 1% with adrenaline. Acta Anaesthesiol Scand 1984; 28: 99-105.

27. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesthesiology. 2009; 111: 25-29.

28. Imasogie N, Ganapathy S, Singh S, Armstrong K, Armstrong P. A prospective, randomized, double-blind comparison of ultrasound-guided axillary brachial plexus blocks using 2 versus 4 injections. Anesth Analg 2010; 110: 1222-1226.

29. Tran de QH, Pham K, Dugani S, Finlayson RJ. A prospective, randomized comparison between double-, triple-, and quadruple-injection ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med 2012; 37: 248-253.

30. Bernucci F, Gonzalez AP, Finlayson RJ, Tran de QH. A prospective, randomized comparison between perivascular and perineural ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med 2012; 37: 473-477.

Chapter 3

Study 1:

Effect of lidocaine volume on the duration of axillary brachial plexus block: a randomised controlled trial

3.1 Abstract

Background: Ultrasound guidance has led to marked improvement in the efficacy of peripheral nerve blocks and a reduction in injectate dose. Although a variety of doses/volumes of local anaesthetic are currently used successfully, the effects of dose reduction on the block characteristics remain unclear. The purpose of our study was to compare the effect of two volumes of lidocaine 2% with epinephrine on the duration of ultrasound-guided axillary brachial plexus block.

Methods: Patients were randomised to receive an ultrasound guided axillary brachial plexus block with either 10 (Group 10) or 30 (Group30) mL of lidocaine 2% with epinephrine. Onset time, duration of sensory and motor block were recorded.

Results: Fifteen patients were randomized to each group. The median [IQR] overall onset time of sensory and motor block was significantly shorter in Group 30 when compared to Group 10 (10 [5 – 15] min vs 15 [10 – 15] min; P = 0.045) and (5 [5 – 10] min vs 10 [10 – 15] min; P = 0.013), respectively. The median overall duration of sensory block was 188 (IQR, 173-205) min in Group 30 versus 165 (IQR, 142-172) min in Group 10 (P <0.001). The median overall duration of motor block was 195 (IQR, 175-220) min in Group 30 versus 165 (IQR, 147-180) min in Group 10 (P=0.001). The median time to first request of supplementary analgesia was 267 (IQR, 224-313) min in Group 30 versus 188 (IQR, 168-224) mins in Group 10 (P= 0.011).

Conclusion: Ultrasound-guided axillary brachial plexus block performed with 10 mL versus 30 mL of lidocaine 2% with epinephrine resulted in shorter overall block duration and shorter time to first request of rescue analgesia.

3.2 Introduction

With the advent of ultrasound guidance, there has been marked improvement in the characteristics of the peripheral nerve blocks compared to alternative techniques. Ultrasound guidance has been shown to improve block success rate,[1-4] to shorten onset time,[5-7] and to afford a reduction in the local anaesthetic dose.[8-11]

Ultrasound-guided axillary brachial plexus block is an effective and widely used technique for providing surgical anaesthesia at and below the elbow. Traditionally, higher volumes of local anaesthetic[1,12,13] have been administered to achieve successful axillary brachial plexus block. Many studies have demonstrated that similar efficacy can be achieved with volumes as low as 2-4 mL lidocaine 1.5%[14] or even 1 mL of lidocaine 2% per nerve.[22] Although reducing the dose of local anaesthetic can potentially reduce the incidence of complications, the effect of dose reduction on the block characteristics in general, and on block duration in particular, remains unclear. Previously, studies comparing block duration and onset time when using different doses of local anaesthetic yielded conflicting results.

We hypothesised that a lower volume (dose) of a given concentration of local anaesthetic solution results in a shorter block duration following ultrasound guided axillary brachial plexus block. In order to test this hypothesis, we carried out a prospective, randomised, single-blinded clinical trial comparing block duration following performance of an axillary brachial plexus block with 10 and 30 mL of lidocaine 2% with epinephrine, respectively.

3.3 Methods

This single centre study was approved by the Clinical Research Ethics Committee of Cork Teaching Hospitals, Cork, Ireland [ECM 4(j) 02/10/12; 20 September 2012, Chairperson Dr Michael Hyland], registered at https://clinicaltrials.gov (NCT03163472), and carried out at Cork University Hospital. Having obtained written informed consent from each, patients aged 18 years or older, ASA grade I-III undergoing unilateral upper limb trauma surgery (operative fixation of fractures distal to the elbow) were enrolled in the study. Exclusion criteria were contraindication to regional anaesthesia, hypersensitivity to amide local anaesthetics, intolerance or contraindication to non-steroidal anti-inflammatory drugs, BMI > 35, pregnancy, cardiac conduction abnormalities, history of hepatic and renal insufficiency, chronic pain, peripheral neuropathy, and psychiatric disorder.

Patients were randomised using simple randomisation, computer generated numbers and sealed envelope technique, prepared by an investigator with no clinical involvement in the trial. They were subsequently allocated to receive ultrasound-guided axillary brachial plexus block with either 10 mL or 30 mL lidocaine 2% with 1:200,000 epinephrine. Intravenous access was established in the contralateral upper limb and standard monitoring was employed throughout the procedure. The operative arm was abducted and externally rotated with the elbow flexed at 90˚. Under aseptic precautions the axillary brachial plexus block was performed under ultrasound guidance alone using a SonoSite Titan unit (SonoSite®, Bothwell, WA) with a 38 mm linear array 5–10 MHz transducer (L38). After identifying the median, ulnar, radial, and musculocutaneous nerves in the axillary region, a 50 mm 24-gauge insulated short bevel needle (Stimuplex® B. Braun, Melsungen, Germany) was advanced in-plane towards each nerve with the aim of surrounding it with either

2.5mL (10 mL group) or 7.5 mL (30 mL group) lidocaine 2% with epinephrine 1:200,000. Dynamic manipulation of the needle was sought to facilitate the circumferential perineural spread of local anaesthetic. All blocks were performed by an operator experienced in the ultrasound-guided peripheral nerve blocks.

Block assessment

Upon completion of the block, a blinded observer unaware of the injectate volume assessed the onset of sensory and motor block[15] in the innervation area of each nerve (median, ulnar, radial, and musculocutaneous nerve) every 5 mins, until surgical anaesthesia was achieved or 30 mins have elapsed. Sensory function was scored as being present or absent and motor function was graded using the modified Bromage Scale (Table 1). Surgical anaesthesia was defined as a motor score ≤2, with absent sensation to cold (tested with ethyl chloride BP, Criogesic®, Dr Georg Friedrich Henning, Chemische Fabrik Walldorf GmbH, Walldorf, Germany). Each nerve distribution area was individually assessed, and the onset time was measured from conclusion of the block (removal of block needle, $\mathbf{T_0}$) to attainment of surgical anaesthesia. The block was considered a failure if surgical anaesthesia had not been achieved at 30 mins in one or more of the four nerve distribution areas. In case of block failure, an additional rescue block or conversion to general anaesthesia was planned with the view of analysing data from those patients separately. All patients received paracetamol 1 g and diclofenac sodium 75 mg iv intraoperatively. In case of patient discomfort or upon request, sedation with midazolam to a maximum of 3 mg and/or supplemental analgesia with up to 100 ug fentanyl was provided by the attending anaesthesiologist.

Postoperative analgesia was prescribed around the clock in the form of paracetamol 1 g po 6 hourly and diclofenac 75 mg po 12 hourly. Oxycodone 10 mg orally 4-6 hourly was administered as rescue analgesia. Postoperatively, recovery of sensory and motor function of each nerve was assessed every 15 mins by a blinded observer. Block regression was defined as a return of sensation to cold and motor power (score ≥3) in any nerve distribution area.

The primary outcome was overall duration of sensory block, which was defined as the time elapsed from T_0 until the return of sensation in any one or more of the four nerve distribution areas. Similarly, overall duration of motor block was defined as the time interval from T_0 to return of motor power (score ≥3) in any one or more of the four nerve distribution areas. Secondary outcome measures included overall duration of motor block, duration of sensory and motor block of individual nerves, onset time of sensory and motor block, time to first request of postoperative opioid analgesia and incidence of adverse effects perioperatively.

Sample size and statistical analysis

The sample size was calculated based on the overall duration of sensory block as the primary outcome parameter. Kaabachi et al[16] found a mean duration of sensory block of 126 (SD ± 48) min following an axillary brachial block performed with 30 mL lidocaine 1.5%. The minimum sample size required to have a 90% probability of detecting a decrease in duration of 60 mins (level of significance 0.05) was 13 patients per group. We recruited 15 patients per group to account for potential dropouts.

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York). The Shapiro-Wilk test was used for normality testing. Continuous, normally

distributed data are presented as mean (SD), and non-normally distributed data as median (interquartile range [IQR]). Comparisons between groups were analysed using the unpaired Student's t test for normally distributed data and the Mann-Whitney U test for nonparametric data. Categorical variables were compared between groups using Pearson's or Fischer's exact test. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

3.4 Results

Thirty patients were enrolled in the study (15 in each group) from November 2012 to August 2013. All patients completed the study, thus data from 30 patients was analysed (Fig 1). Patient characteristics were similar in the two groups (Table 2). The overall onset time of sensory and motor block were shorter in Group 30 compared to Group 10 (Table 3). This was reflected in the individual nerve block onset times with the exception of radial sensory and musculocutaneous motor block onset (Table 3). The overall duration of sensory and motor block was longer by 12% and 15% respectively in Group 30. (Table 4). In addition, the overall duration of both sensory and motor block of individual nerves were longer in Group 30 (Table 4). Figure 2 depicts the primary outcome measure, overall duration of sensory block. Figure 3 represents overall duration of motor block.

No patient required a rescue block, conversion to general anaesthesia, or intraoperative opioid analgesia. Seven patients, three in Group 10 and 4 in Group 30 received intraoperative sedation for anxiety. Twenty patients, 12 in Group 10 and 8 in Group 30, requested additional opiate analgesia postoperatively. The median (IQR) time to first request of supplementary analgesia was longer in Group 30 at 267 (224-313) min when compared to 188 (168-224) min in Group 10 (P= 0.011). There were no adverse events noted in either group.

3.5 Discussion

The most important finding of this study is that the reduction in volume (dose) of local anaesthetic resulted in shorter overall duration of sensory and motor block and a shorter time to first request of postoperative analgesia.

Previously, studies have shown that, ultrasound guidance can significantly reduce the volume of local anaesthetic required to achieve successful nerve blocks when compared to conventional techniques[8-10]. Use of large volumes of local anaesthetic is associated with increased incidence of complications e.g., systemic toxicity of local anaesthetics[17,18] and inadvertent phrenic nerve block during interscalene block leading to respiratory impairment[19]. Given the potential advantage of reducing adverse events, it would be prudent to use lower volume of local anaesthetic to achieve successful nerve blocks without affecting the desirable characteristics of the block (i.e., the duration of block)

Few studies have evaluated specifically the effect of volume on the duration of block. Ponrouch et al[20] studied the minimum effective anaesthetic volume of mepivacaine 1.5% for median and ulnar nerve block and found a significant correlation between lower volume and shorter duration of sensory block but no effect on block onset time. Similarly, Schoenmakers et al[21] compared the effect of local anaesthetic volume 15 mL vs 40 mL mepivacaine 1.5% on the duration of ultrasound guided axillary brachial block. They found the sensory and motor block duration was 17% and 19% shorter, respectively in the lower volume group. Our study showed similar outcomes. In the high-volume group, we used 30 mL as opposed to 40 mL used in previous studies. This is because with the advent of ultrasound, volume of more than 30 mL is rarely used for axillary brachial plexus block.

A number of studies have demonstrated that successful ultrasound guided axillary brachial plexus block can be achieved with very low volumes. Harper et al[14] were able to surround each nerve of the axillary brachial plexus using 2-4 mL of lidocaine 1.5% with epinephrine 1:200,000. Their mean (95% CI) duration of sensory block of 137.1 (105.6-168.7) min was similar to that in our Group 10. Similarly, O'Donnell et al[22] have successfully achieved axillary brachial plexus block with 1 mL of lidocaine 2% with epinephrine 1: 200, 000 per nerve (total 4 mL). Their mean block duration of 160.8 (SD ± 30.7) min was not dissimilar to that in our Group 10. We used 10 ml in this lower volume group as opposed to smaller volumes as we believe this dose (volume and concentration) reflects the current clinical practice of ultrasound guided axillary block more closely. Our study supports the correlation between the volume of anaesthetics and duration of peripheral nerve block, with lower volumes resulting in shorter duration.

The strengths of our study lie with its design and rigorous methodology geared towards detecting resolution of sensory and motor block. The clinical implication of this is far reaching. Not only should we aim for surgical anaesthesia grade nerve blocks for the duration of the operation, but we should be able to predict the dissipation of sensory block in particular. This is important for both patient expectations management and timing of analgesia such as to minimise or eliminate rebound pain.

Our study has limitations such as the modest sample size, and the 15 min interval assessment of the residual block, thus potentially missing the precise resolution and overestimating block duration. Had we in addition assessed pain scores following

resolution of the block, we could have estimated the magnitude of rebound pain. This is an area that deserves further investigation.

3.6 Conclusion

When compared to 30 mL, using 10 mL lidocaine 2% with epinephrine for ultrasound-guided axillary brachial plexus resulted in shorter overall duration of sensory and motor block, a shorter time to first postoperative analgesia request, and a longer sensory and motor block onset time.

3.7 Tables

Table 1. Motor and sensory testing

	Motor test	**Sensory test site**
Median	Flexion of radial 3 fingers	Thenar eminence
Radial	Extension of wrist/elbow	Dorsum of hand
Ulnar	Abduction of fingers	Hypothenar eminence
Musculocutaneous	Elbow flexion	Over base first metacarpal

Modified Bromage Scale

Score	Definition
4	Full power in relevant muscle.
3	Reduced power but ability to move muscle against resistance
2	Ability to move relevant muscle group against gravity but not against resistance
1	Flicker of movement in relevant muscle group
0	No movement in relevant muscle group

Table 2: Patient characteristics

Continuous variables are presented as means (SD), categorical variables as counts

y = years, n=number

	Group 10 mL (n=15)	**Group 30 mL (n=15)**	**P value**
Age, y	49 ± 15.1	50 ± 22.1	0.91
Sex, M/F, n	8/7 (53%/47%)	9/6 (60%/40%)	0.71
BMI, Kg/m^2	25.7 ± 3.1	27.1 ± 2.9	0.21
ASA grade (I/II/III), n	7/7/1 (47%, 47%, 6%)	7/8/0 (47%, 53%)	0.59
Duration of surgery, min	55.13 ± 19.2	55.33 ± 9.3	0.97
Site of surgery (forearm, wrist, hand),n	0/13/2	1/11/3	0.50

Table 3. Sensory and motor block onset time

Data are presented in minutes, values are median (interquartile range, Q1-Q3)

	Group 10 mL	**Group 30 mL**	**P value**
Overall sensory onset	15 (10-15)	10 (5-15)	0.045
Overall motor onset	10 (10-15)	5 (5-10)	0.013
Radial nerve			
Sensory	15 (10-15)	5 (5-15)	0.053
Motor	10 (5-15)	5 (5-5)	0.016
Ulnar nerve			
Sensory	10 (5-15)	5 (5-5)	0.012
Motor	10 (10-15)	5(5-10)	0.005
Median nerve			
Sensory	10 (5-15)	5 (5-10)	0.019
Motor	10 (5-15)	5 (5-5)	0.001
Musculocutaneous nerve			
Sensory	10 (5-10)	5 (5-5)	0.006
Motor	10 (5-10)	5 (5-5)	0.087

Table 4. Sensory and motor block duration

Data are expressed in minutes, values are median (Interquartile range, Q1-Q3)

*****Difference = difference between the median of Group 30 and Group 10 as a percentage of the median value of Group 30

	Group 10 mL (n=15)	**Group 30 mL (n=15)**	**P value**	**Difference, * %**
Overall sensory duration	165 (142-172)	188 (173-205)	<0.001	12
Overall motor duration	165 (147-180)	195 (175-220)	0.001	15
Radial nerve				
Sensory	165 (147-185)	195 (173-218)	0.001	15
Motor	172 (147-185)	204 (185-225)	0.001	16
Ulnar nerve				
Sensory	165 (151-185)	195 (179-220)	0.002	15
Motor	166 (152-185)	205 (188-235)	<0.001	19
Median nerve				
Sensory	169 (143-180)	190 (179-220)	<0.001	11
Motor	169 (147-187)	195 (182-235)	0.005	13
Musculocutaneous nerve				
Sensory	165 (147-185)	195 (185-230)	0.002	15
Motor	166 (157-185)	210 (182-235)	0.001	20

3.8 Figures

Figure 1. Consort flow diagram

n = number

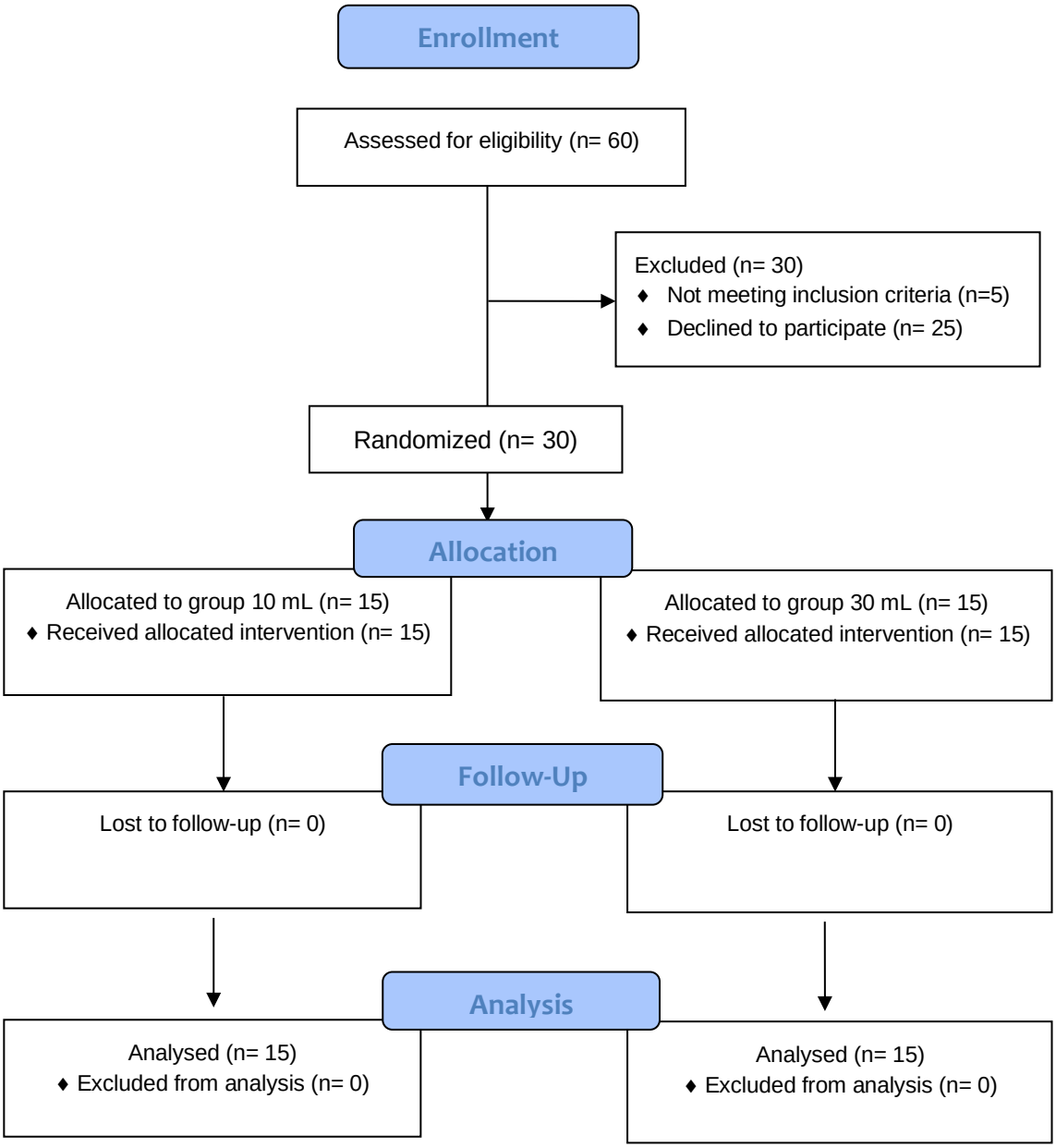


Figure 2. Overall duration of sensory block

The horizontal black line represents the median, the box represents the interquartile range, and the vertical lines show the lowest and highest values.

*P<0.001

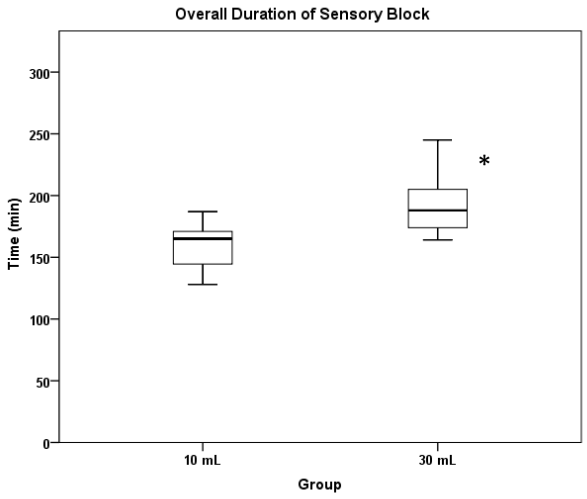
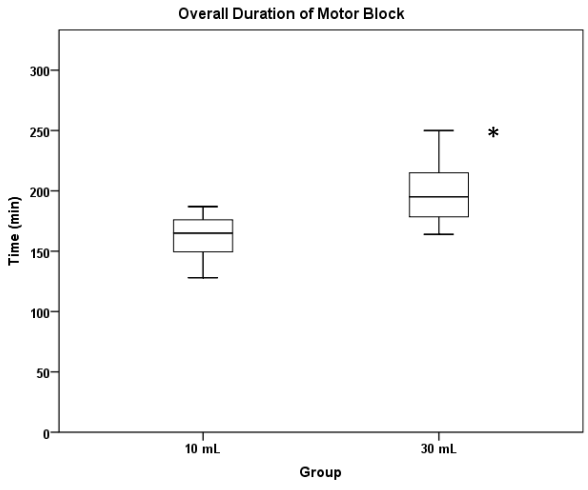


Figure 3. Overall duration of motor block

The horizontal black line represents the median, the box represents the interquartile range, and the vertical lines show the lowest and highest values.

*P=0.001



3.9 References for chapter 3

1. Chan VW, Perlas A, McCartney CJ, Brull R, Xu D, Abbas S. Ultrasound guidance improves success rate of axillary brachial plexus block. Can J Anaesth 2007;54:176-182.
2. Williams SR, Chouinard P, Arcand G, et al. Ultrasound guidance speeds execution and improves the quality of supraclavicular block. Anesth Analg 2003;97:1518-23.
3. Kapral S, Greher M, Huber G, et al. Ultrasonographic guidance improves the success rate of interscalene brachial plexus blockade. Reg Anesth Pain Medicine 2008;33:253-8.
4. Sites BD, Beach ML, Spence BC, et al. Ultrasound guidance improves the success rate of a perivascular axillary plexus block. Acta Anaesthesiol Scand 2006;50:678-84.
5. Marhofer P, Schrogendorfer K, Koinig H, Kapral S, Weinstabl C, Mayer N. Ultrasonographic guidance improves sensory block and onset time of three-in-one blocks. Anesth Analg 1997;85:854-7.
6. Lo N, Brull R, Perlas A, et al. Evolution of ultrasound guided axillary brachial plexus blockade: retrospective analysis of 662 blocks. Can J Anaesth 2008;55:408-13.
7. Casati A, Danelli G, Baciarello M, et al. A prospective, randomized comparison between ultrasound and nerve stimulation guidance for multiple injection axillary brachial plexus block. Anesthesiology 2007;106:992-6.
8. Abrahams MS, Aziz MF, Fu RF, Horn JL. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic

review and meta-analysis of randomized controlled trials. Br J Anaesth 2009;102:408-17.

9. McNaught A, Shastri U, Carmichael N, et al. Ultrasound reduces the minimum effective local anaesthetic volume compared with peripheral nerve stimulation for interscalene block. Br J Anaesth 2011;106:124-30.

10. Casati A, Baciarello M, Di Cianni S, et al. Effects of ultrasound guidance on the minimum effective anaesthetic volume required to block the femoral nerve. Br J Anaesth 2007;98:823-7.

11. Danelli G, Ghisi D, Fanelli A, et al. The effects of ultrasound guidance and neurostimulation on the minimum effective anesthetic volume of mepivacaine 1.5% required to block the sciatic nerve using the subgluteal approach. Anesth Analgesia 2009;109:1674-8.

12. Serradell A, Herrero R, Villanueva JA, Santos JA, Moncho JM, Masdeu J. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. Br J Anaesth 2003;91:519-24.

13. Koscielniak-Nielsen ZJ, Hesselbjerg L, Fejlberg V. Comparison of transarterial and multiple nerve stimulation techniques for an initial axillary block by 45 mL of mepivacaine 1% with adrenaline. Acta Anaesthesiol Scand 1998;42:570-5.

14. Harper GK, Stafford MA, Hill DA. Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound-guidance: a pilot study. Br J Anaesth 2010;104:633-6.

15. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesthesiology 2009;111:25-9.

16. Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Ben Abdelaziz A. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. Anesth Analg 2009;108:367-70.

17. Ichikawa M, Ishiyama T, Shibuya K, Okawa I, Matsukawa T. [Grand mal convulsion after an interscalene block with ropivacaine]. Masui 2009;58:467-9.

18. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. Anesth Analg 1995;81:321-8.

19. 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. Br J Anaesth 2008;101:549-56.

20. Ponrouch M, Bouic N, Bringuier S, et al. Estimation and pharmacodynamic consequences of the minimum effective anesthetic volumes for median and ulnar nerve blocks: a randomized, double-blind, controlled comparison between ultrasound and nerve stimulation guidance. Anesth Analg 2010;111:1059-64.

21. Schoenmakers KP, Wegener JT, Stienstra R. Effect of local anesthetic volume (15 vs 40 mL) on the duration of ultrasound-guided single shot

axillary brachial plexus block: a prospective randomized, observer-blinded trial. Reg Anesth Pain Med 2012;37:242-7.

22. O'Donnell B, Riordan J, Ahmad I, Iohom G. Brief reports: a clinical evaluation of block characteristics using one milliliter 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesth Analg 2010;111:808-10.

Chapter 4

Study 2:

Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled study

4.1 Abstract

Background: Ultrasound guidance has led to marked improvement in the success rate and characteristics of peripheral nerve blocks. However, effects of varying the volume or concentration of a fixed local anaesthetic dose on nerve block remains unclear. The purpose of our study was to evaluate whether at a fixed dose of lidocaine, altering the volume and concentration will have any effect on the onset time of ultrasound-guided axillary brachial plexus block.

Material and methods: Twenty patients were randomised to receive an ultrasound-guided axillary brachial plexus block with either lidocaine 2% with epinephrine (20 ml, Group 2%) or lidocaine 1% with epinephrine (40 ml, Group 1%). The primary endpoint was block onset time. Secondary outcomes included duration of the block, performance time, number of needle passes, incidence of paraesthesia and vascular puncture.

Results: The median [IQR] onset time of surgical anaesthesia was shorter in Group 1% when compared to Group 2% (6.25 [5 – 7.5] min vs 8.75 [7.5 – 10] min; P = 0.03). The mean (SD) overall duration of surgical anaesthesia was significantly shorter in Group 1% compared to Group 2% (150.9 ± 17.2 min vs 165.1 ± 5.9 min; P = 0.02). Group 1% had a shorter performance time with fewer needle passes. The incidence of vascular puncture and paraesthesia was similar in the two groups.

Conclusion: In ultrasound-guided axillary brachial plexus block, administering a higher volume of lower concentration lidocaine is associated with shorter onset time and duration of surgical anaesthesia.

4.2 Introduction

Ultrasound-guided axillary brachial plexus block (USgABPB) is an effective and reliable technique for the provision of surgical anaesthesia for forearm and hand surgeries.[1-4] Previously, numerous studies have compared efficacy of brachial plexus block using different local anaesthetic solutions of varying concentrations and volumes.[5-7] However, only few studies have shown that, at constant dose, altering the volume or concentration can affect the characteristics of the nerve block. Historically, it has been reported that higher concentration/lower volume yielded a shorter onset time when compared to higher volume/lower concentration solution using a single injection nerve stimulation technique for sciatic nerve block.[8,9] In contrast, in perivascular axillary blocks with a fixed dose of local anaesthetic, larger volumes provided a better quality sensory[10] and quicker onset motor block[11] when compared to lower volumes. The results from these studies were inconsistent with respect to onset time, success rate and duration of the block. In addition, it is unknown whether they can be replicated with ultrasound guidance.

In this prospective, randomised, double-blind study, we examined whether two different volumes and concentrations of a fixed dose of lidocaine with epinephrine influenced the characteristics of USgABPB. We hypothesised that 40 mL of lidocaine 1% with epinephrine would result in a shorter onset time when compared to 20 mL of lidocaine 2% with epinephrine.

4.3 Methods

This single centre study was approved by the Clinical Research Ethics Committee of Cork Teaching Hospitals, Cork, Ireland [ECM 4(mm) 01/07/14; 01 July 2014, Chairperson Professor Michael G Molloy], registered at https://clinicaltrials.gov (NCT03207035), and carried out at Cork University Hospital. Having obtained written informed consent from each, patients aged 18 years or older, ASA grade I-III scheduled to undergo unilateral upper limb trauma surgery of the hand or forearm, were enrolled in the study. Exclusion criteria were contraindication to regional anaesthesia, hypersensitivity to amide local anaesthetics, intolerance, or contraindication to non-steroidal anti-inflammatory drugs, BMI > 35, pregnancy, cardiac conduction abnormalities, history of hepatic and renal impairment, chronic pain, neuromuscular disease, and psychiatric disorder.

Patients were randomised using computer-generated sequence of random numbers and sealed envelope technique, prepared by an investigator with no clinical involvement in the trial. They were subsequently allocated to receive USgABPB with either 20 mL lidocaine 2% with 1:200,000 epinephrine (Group 2%) or 40 mL lidocaine 1% with 1:400,000 epinephrine (Group 1%) (diluted up to the study volume with 0.9% saline). Intravenous access was established in the contralateral upper limb and standard monitoring was employed throughout the procedure. The operative arm was abducted and externally rotated with the elbow flexed at 90˚. Under aseptic precautions the axillary brachial plexus block was performed under ultrasound guidance alone using a SonoSite Titan unit (SonoSite®, Bothwell, WA) with a 38 mm linear array 5–10 MHz transducer (L38). Following the identification of the median, ulnar, radial, and musculocutaneous nerves in the axillary region, a 50

mm 24-gauge insulated short bevel needle (Stimuplex® B. Braun, Melsungen, Germany) was advanced in-plane towards each nerve with the aim of surrounding it with either 5 mL (Group 2%) or 10 mL (Group 1%) of local anaesthetic solution. Dynamic manipulation of the needle was sought to facilitate the circumferential perineural spread of local anaesthetic. All blocks were performed by an operator experienced in USgABPB.

Block assessment

Upon completion of the block, a blinded observer not aware of the injectate volume, assessed the onset of sensory and motor block in the innervation area of each nerve (median, ulnar, radial, and musculocutaneous nerve) every 2.5 mins, until surgical anaesthesia was achieved, or 30 mins have elapsed. Sensory function was scored as being present or absent and motor function was graded using the modified Bromage Scale[4] (Table1 page 50). Surgical anaesthesia was defined as a motor score ≤2, with absent sensation to cold (tested with ethyl chloride BP, Criogesic®, Dr Georg Friedrich Henning, Chemische Fabrik Walldorf GmbH, Walldorf, Germany). Each nerve distribution area was individually assessed, and the sensory and motor onset time was measured separately from conclusion of the block (removal of block needle, T_0) to attainment of absent sensation to cold and a motor score ≤2, respectively. Overall sensory and motor block onset time was taken from T_0 to attainment of surgical anaesthesia in all innervation territories. The block was considered a failure if surgical anaesthesia had not been achieved at 30 mins in one or more of the four nerve distribution areas. In case of block failure, an additional rescue block or conversion to general anaesthesia was planned together with separate analysis of data from those patients. All patients received paracetamol 1 g and diclofenac sodium 75 mg iv intraoperatively. In case of patient discomfort or upon

request, sedation with midazolam to a maximum of 3 mg and/or supplemental analgesia with up to 100 ug fentanyl was provided at the discretion of the attending anaesthesiologist.

Postoperative analgesia was prescribed around the clock in the form of paracetamol 1 g po 6 hourly and diclofenac 75 mg po 12 hourly. Oxycodone 10 mg orally 4-6 hourly as required was administered as rescue analgesia. Postoperatively, sensory and motor function of each nerve was assessed every 15 mins. Sensory and motor duration was measured separately for each nerve from T_0 to return of sensation to cold and motor power to ≥3, respectively. Overall sensory and motor block offset was defined as return of sensation to cold and motor power (score ≥3) respectively, in any one nerve distribution area.

The primary outcome was overall surgical anaesthesia onset time, which was defined as the time elapsed from conclusion of block (T_0) until attainment of surgical anaesthesia in all nerves distribution areas. Secondary outcome measures included overall duration of sensory and motor block, as well as sensory and motor onset times and durations of individual nerves. Overall duration of surgical anaesthesia was defined as time elapsed from T_0 to return of sensation and motor power (score ≥3) respectively in any one nerve distribution area.

Block performance parameters were recorded such as *imaging time* (defined as time elapsed from placement of US probe on the patient to acquisition of a satisfactory image of the axillary artery and surrounding nerves) and *needling time* (defined as the time interval between insertion and removal of block needle). Thus, *performance time* was defined as the sum of imaging and needling times. The number of needle passes were recorded. The initial needle pass was considered as the first pass and any

subsequent needle advancement preceded by retraction of 1cm counted as an additional pass. Incidences of vascular puncture and paraesthesia were also noted.

Sample size and statistical analysis

In the absence of data from previous studies using 20 ml of lidocaine 2% with epinephrine for ultrasound guided axillary brachial plexus block, sample size was calculated based on our pilot study of 10 patients. We found a mean (SD) onset time of 11.25 (± 2.3) min. The minimum sample size required to have an 80% probability of detecting a 30% decrease in onset time (level of significance 0.05) was 7 patients per group. We recruited 10 patients per group to account for potential dropouts.

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York). The Shapiro-Wilk test was used for normality testing. Continuous, normally distributed data are presented as mean (SD), and non-normally distributed data as median (interquartile range [IQR]). Comparison between groups were analysed using the unpaired Student's t test for normally distributed data and the Mann-Whitney U test for nonparametric data. Categorical variables were compared between groups using Pearson's or Fischer's exact test. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

4.4 Results

Twenty patients (10 in each group) were recruited to the study from September 2014 to August 2015. All patients completed the study (Fig 1), and none of the patients required rescue block, conversion to general anaesthesia or intraoperative opioid analgesia. There were no adverse events noted in either group. The patient demographic characteristics were similar between the groups (Table 1). Table 2 details onset times. The median [IQR] overall onset time of surgical anaesthesia was shorter in Group 1% compared to Group 2%. The overall onset time of sensory but not motor block was also shorter in Group 1%. Onset times of individual nerves were similar in the two groups, with the exception of median sensory onset time which was shorter in Group 1%. Table 3 depicts block durations. The mean (SD) overall duration of surgical anaesthesia was shorter in Group 1% compared to Group 2%, reflective of overall motor block duration. Individual sensory and motor block durations were similar, with median motor block duration shorter in Group 1%. Figure 2 shows the primary outcome measure, overall onset of surgical anaesthesia.

Group 1% had a shorter needling time; performance time and fewer needle passes when compared to Group 2%. No difference was found between the groups with respect to imaging time, incidence of vascular puncture or paraesthesia (Table 4).

4.5 Discussion

In this single centre randomised controlled trial, we observed that when using 400 mg of lidocaine with epinephrine, increasing the volume of injectate by dilution resulted in shorter overall onset time and subsequent shorter duration of ultrasound guided axillary brachial plexus block. While the shorter onset may be advantageous and desirable in clinical settings with high volume activity and quick turnover, it appears to come at the expense of a shorter duration of block which should be both anticipated and managed appropriately.

In theory, both concentration and volume of the perineural injectate can influence the characteristics of the nerve block. Higher concentrations may shorten the onset time by facilitating the diffusion of local anaesthetic molecules into the nerve,[9] while larger volumes may influence the block onset time by promoting injectate spread around neural structures.[11] However, how the volume/concentration ratio at a fixed local anaesthetic dose affects the characteristics of a nerve block, remains unclear. Previous studies yielded inconsistent results with respect to success rate, onset time and duration of the block.[8-16] Several factors such as local anaesthetic volume/concentration ratio, anatomical site of injection and the nerve locating technique used in the study might have contributed to the variable results.

For the Labat approach to the sciatic nerve block using a single injection nerve stimulation technique, Taboada et al observed that 20 mL of mepivacaine 1.5% (vs 30 mL of mepivacaine 1%) improved the success rate and shortened the onset time of both sensory and motor block.[9] The authors speculated that, because of the size of sciatic nerve and the thickness of epineurium it would require a large concentration gradient to facilitate the diffusion of local anaesthetic molecules. In contrast,

Cappelleri et al, using a double injection nerve stimulator technique for sciatic nerve block, found no difference with respect to success rate, onset time and duration of the block between 12 mL of mepivacaine 2% and 24 mL of mepivacaine 1%.[14] They hypothesized that compared to a single injection technique, the double injection resulted in better distribution of local anaesthetic around each component of the peripheral nerve and with this, the effect of local anaesthetic volume/concentration ratio become secondary to the regional nerve localisation technique.

Similarly, few studies have evaluated the effect of altering the volume and concentration of a fixed local anaesthetic dose for the brachial plexus block. Krenn et al suggested that higher volume of ropivacaine resulted in faster onset of motor block for a single injection axillary block, where loose connective tissue surrounds the brachial plexus.[11] In contrast, studies where the axillary block was performed using the multiple injection nerve stimulator technique[12] and infraclavicular block using ultrasound,[13] did not show any difference with respect to block success rate and onset time. In our study, overall onset of surgical anaesthesia was faster using a higher volume when compared to a lower volume (identical dose), and this was mainly reflective of the onset of sensory but not motor component of the block. The difference in the result could be explained by the technique used to locate the target nerves. We performed the ultrasound guided axillary brachial plexus block having identified all four terminal nerves with the precise endpoint consisting of circumferential perineural spread of local anaesthetic, and not using a single or multiple nerve stimulation, or ultrasound guided perivascular approach.[3,17]

Interestingly, and perhaps counterintuitively, the injection of the lower volume resulted in a longer block performance time. This is likely due to the requirement for

a more precise needle tip positioning and subsequent adjustment in order to achieve circumferential spread around each of the four terminal nerves while having a limited injectate volume at disposal.

Our study is limited inter alia by the small sample size. Although we found differences between groups in terms of both onset time and duration of block, these results cannot be generalised to other local anaesthetics, techniques, and peripheral injection sites due to variation in the anatomical architecture surrounding nerves.[18-20] It has been demonstrated that, using a multiple injection technique for a humeral canal block, higher volume and lower concentration of levobupivacaine improved the sensory block quality and success rate.[15] In contrast, ultrasound guided interscalene block resulted in faster onset of block using lower volume and higher concentration of ropivacaine.[16]

4.6 Conclusion

In conclusion, when compared to 20 mL of lidocaine 2% with epinephrine, 40 mL of lidocaine 1% with epinephrine resulted in faster overall onset and shorter duration of surgical anaesthesia following an ultrasound guided axillary brachial plexus block. Further studies are required to determine whether these results can be extrapolated to other local anaesthetics and anatomical injection sites.

4.7 Tables

Table 1: Patient characteristics

Continuous variables are presented as means (SD), categorical variables as counts

y = years, n=number

	Group 2% (n=10)	**Group 1% (n=10)**	**P Value**
Age, y	46.8 ± 18.2	48 ± 15.7	0.88
Sex, M/F, n	7/3	8/2	0.60
BMI, Kg/m^2	25.3 ± 3.2	24.5 ± 3.6	0.62
ASA grade (I/II/III), n	7/3/0	4/6/0	0.18
Duration of surgery, min	62 ± 10.8	58.5 ± 14.9	0.56
Site of surgery (forearm, wrist, hand), n	0/5/5	0/6/4	0.65

Table 2. Sensory and motor block onset time

Data are presented in minutes, values are median (interquartile range, Q1-Q3)

	Group 2% (n=10)	**Group 1% (n=10)**	**P value**
Overall sensory onset	8.75 [5 – 10]	5 [5 – 7.5]	0.046
Overall motor onset	6.25 [5 – 7.5]	5 [2.5 – 7.5]	0.41
Overall onset of surgical anaesthesia	8.75 [7.5 – 10]	6.25 [5 – 7.5]	0.03
Radial nerve			
Sensory	5 [5 – 10]	5 [2.5 – 7.5]	0.12
Motor	5 [2.5 – 7.5]	3.75 [2.5 – 5]	0.55
Ulnar nerve			
Sensory	6.25 [5 – 7.5]	5 [2.5 – 5]	0.12
Motor	5 [2.5 – 7.5]	5 [2.5 – 7.5]	0.87
Median nerve			
Sensory	6.25 [5 – 10]	5 [2.5 – 5]	0.03
Motor	5 [2.5 – 7.5]	5 [2.5 – 5]	0.93
Musculocutaneous nerve			
Sensory	5 [5 – 10]	3.75 [2.5 – 5]	0.10
Motor	3.75 [2.5 – 5]	5 [2.5 – 5]	0.87

Table 3. Sensory and motor block duration

Data are expressed in minutes, values are mean ± SD

	Group 2% (n=10)	**Group 1% (n=10)**	**P value**
Overall sensory duration	171.6 ± 7.1	158.4 ± 21.7	0.08
Overall motor duration	165.1 ± 5.9	150.9 ± 17.2	0.02
Overall duration of surgical anaesthesia	165.1 ± 5.9	150.9 ± 17.2	0.02
Radial nerve			
Sensory	176.1 ± 3.7	167.40 ± 20.4	0.20
Motor	170.1 ± 7.2	158.4 ± 18.6	0.08
Ulnar nerve			
Sensory	174.6 ± 3.6	168.9 ± 22.4	0.44
Motor	168.6 ± 8.0	158.4 ± 19.7	0.15
Median nerve			
Sensory	173.1 ± 5.9	162.9 ± 19.9	0.14
Motor	168.1 ± 7.4	152.4 ± 15.4	0.01
Musculocutaneous nerve			
Sensory	173.1 ± 7.8	161.4 ± 19.9	0.10
Motor	166.6 ± 7.3	152.4 ± 20.4	0.05

Table 4. Block performance data

Continuous variables are presented as mean ± SD, categorical variables as count/or percentage

	Group 2% (n=10)	**Group 1% (n=10)**	**P**
Imaging time, min (A)	2.5 ± 0.5	2.4 ± 0.6	0.70
Needling time, min (B)	8.5 ± 1.2	6.7 ± 0.9	0.002
Performance time, mins (A+B)	10.9 ± 1.3	9.1 ± 0.5	0.001
No. needle passes	10.5 ± 2.3	7.2 ± 1.0	0.001
Vascular puncture, n (%)	2 (20)	1 (10)	0.53
Paresthesia, n (%)	4 (40)	2 (20)	0.48

4.8 Figures

Figure 1. Consort flow diagram

n = number

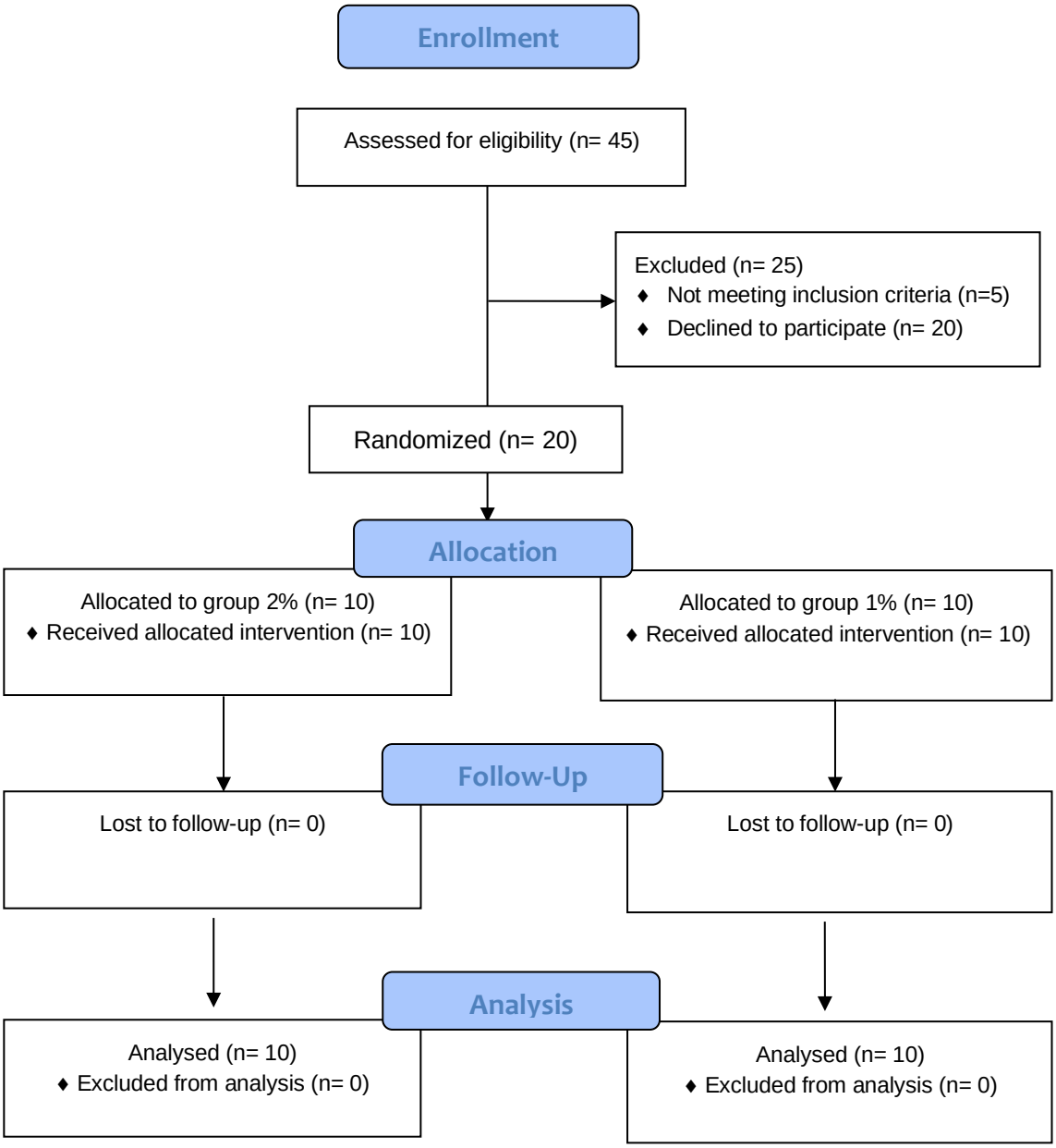
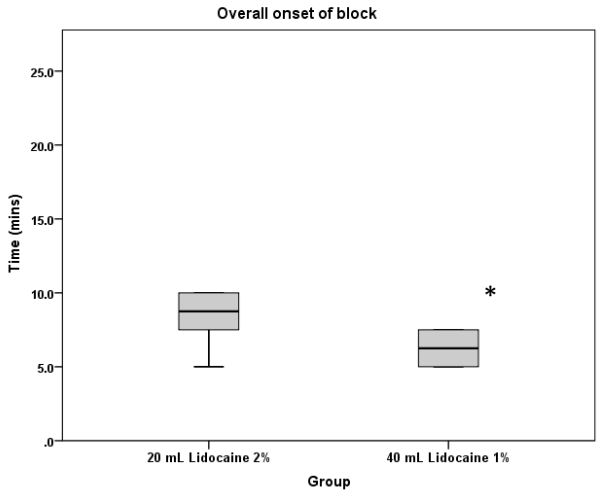


Figure 2. Overall onset of block

The horizontal black line represents the median, the box represents the interquartile range, and the vertical lines show the lowest and highest values.

*P = 0.03



4.9 References for chapter 4

1. Sites BD, Beach ML, Spence BC, et al. Ultrasound guidance improves the success rate of a perivascular axillary plexus block. Acta Anaesthesiol Scand 2006; 50: 678-684.
2. Chan VW, Perlas A, McCartney CJ, et al. Ultrasound guidance improves success rate of axillary brachial plexus block. Can J Anaesth 2007; 54: 176-182.
3. Casati A, Danelli G, Baciarello M, et al. A prospective, randomized comparison between ultrasound and nerve stimulation guidance for multiple injection axillary brachial plexus block. Anesthesiology 2007; 106: 992-996.
4. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesthesiology 2009; 111: 25-29.
5. Vester-Andersen T, Eriksen C, Christiansen C. Perivascular axillary block III: blockade following 40 ml of 0.5%, 1% or 1.5% mepivacaine with adrenaline. Acta Anaesthesiol Scand 1984; 28: 95-98.
6. Serradell A, Herrero R, Villanueva JA, et al. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. Br J Anaesth 2003; 91: 519-524.
7. Casati A, Fanelli G, Aldegheri G, et al. Interscalene brachial plexus anaesthesia with 0.5%, 0.75% or 1% ropivacaine: a double-blind comparison with 2% mepivacaine. Br J Anaesth 1999; 83: 872-875.
8. Smith BE, Siggins D. Low volume, high concentration block of the sciatic nerve. Anaesthesia 1988; 43: 8-11.

9. Taboada Muñiz M, Rodríguez J, Bermúdez M, et al. Low volume and high concentration of local anesthetic is more efficacious than high volume and low concentration in Labat's sciatic nerve block: a prospective, randomized comparison. Anesth Analg 2008; 107: 2085-2088.

10. Vester-Andersen T, Christiansen C, Sørensen M, et al. Perivascular axillary block II: influence of injected volume of local anaesthetic on neural blockade. Acta Anaesthesiol Scand 1983; 27: 95-98.

11. Krenn H, Deusch E, Balogh B, et al. Increasing the injection volume by dilution improves the onset of motor blockade, but not sensory blockade of ropivacaine for brachial plexus block. Eur J Anaesthesiol 2003; 20: 21-25.

12. Bertini L, Palmisani S, Mancini S, et al. Does local anesthetic dilution influence the clinical effectiveness of multiple-injection axillary brachial plexus block?: a prospective, double-blind, randomized clinical trial in patients undergoing upper limb surgery. Reg Anesth Pain Med 2009; 34: 408-413.

13. González AP, Bernucci F, Techasuk W, et al. A randomized comparison between 3 combinations of volume and concentration of lidocaine for ultrasound-guided infraclavicular block. Reg Anesth Pain Med 2013; 38: 206-211.

14. Cappelleri G, Ambrosoli AL, Turconi S, et al. Effect of local anesthetic dilution on the onset time and duration of double-injection sciatic nerve block: a prospective, randomized, blinded evaluation. Anesth Analg 2014; 119: 489-493.

15. Nuñez Aguado D, López Alvarez S, Salamanca Montaña ME, et al. [Brachial plexus block with levobupivacaine at the humeral canal: comparison of a

small volume at high concentration with a large volume at low concentration]. Rev Esp Anestesiol Reanim 2005; 52: 529-535.

16. Zhai W, Wang X, Rong Y, Li M, Wang H. Effects of a fixed low-dose ropivacaine with different volume and concentrations on interscalene brachial plexus block: a randomized controlled trial. BMC Anesthesiol 2016; 16: 80.

17. Bernucci F, Gonzalez AP, Finlayson RJ, Tran DQ. A prospective, randomized comparison between perivascular and perineural ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med 2012; 37: 473-477.

18. Areeruk P, Karmakar MK, Reina MA, Mok LYH, Sivakumar RK, Sala-Blanch X. High-definition ultrasound imaging defines the paraneural sheath and fascial compartments surrounding the cords of the brachial plexus at the costoclavicular space and lateral infraclavicular fossa. Reg Anesth Pain Med 2021 Apr 2:rapm-2020-102304. Epub ahead of print. PMID: 33811182.

19. Cornish PB, Leaper CJ, Hahn JL. The "axillary tunnel": an anatomic reappraisal of the limits and dynamics of spread during brachial plexus blockade. Anesth Analg 2007; 104: 1288-1291.

20. Cornish PB, Leaper C. The sheath of the brachial plexus: fact or fiction? Anesthesiology 2006; 105: 563-565.

Chapter 5

Study 3

Effects of clonidine as adjuvant to lidocaine with epinephrine in ultrasound guided axillary brachial plexus block: a randomised controlled trial

5.1 Abstract

Background: Adjuvants have been widely used with local anaesthetics to improve the characteristics of peripheral nerve blocks. We proposed to evaluate the effects of adding clonidine to lidocaine with epinephrine in ultrasound guided axillary brachial plexus blocks.

Material and methods: Twenty-four patients were randomised to receive an ultrasound-guided axillary brachial plexus block with 20 mL of lidocaine 2% with 1:200,000 epinephrine plus 2 mL of either normal saline 0.9% (Group 1) or a mixture of clonidine 1 µg/kg and normal saline 0.9% (Group 2). The primary endpoint was overall onset time of sensory block. Secondary outcomes included overall onset time of motor block and overall duration of sensory and motor block.

Results: The median [IQR] overall onset time of sensory and motor block was significantly shorter in Group 2 when compared to Group 1 (5 [5 – 7.5] min vs 10 [8.8 – 12.5] min; $P < 0.001$) and (5 [2.5 – 7.5] min vs 7.5 [6.3 – 7.5] min; $P = 0.001$), respectively. The median [IQR] overall duration of sensory and motor block was significantly longer in Group 2 compared to Group 1 (225 [200 – 231] min vs 168 [148 – 190] min; $P < 0.001$) and (225 [208 – 231] min vs 168 [148 – 186] min; $P < 0.001$), respectively.

Conclusion: In ultrasound-guided axillary brachial plexus block, the addition of clonidine to lidocaine with epinephrine resulted in shorter onset time and prolonged duration of sensory and motor block.

5.2 Introduction

Adjuncts to local anaesthetics for peripheral nerve blocks have been widely used to enhance quality and duration of both anaesthesia and postoperative analgesia.[1-4] Previous studies have yielded conflicting results when Clonidine, an α_2-adrenergic agonist, was combined with local anaesthetics for the purpose of peripheral nerve blockade. While several studies on brachial plexus block has demonstrated shorter block onset time and longer duration of anaesthesia,[5-10] other studies have found contrasting results.[11,12]

However, all aforementioned studies comparing block onset time and duration following perineural injection of clonidine and local anaesthetic admixture, used both conventional volumes and techniques for locating nerves. The question arises as to the effect of clonidine as adjuvant to local anaesthetics in the context of ultrasound guidance and relatively lower volumes as per current practice.

In this prospective study, we set out to evaluate the effects of adding both clonidine and epinephrine to lidocaine 2% on the block onset time and duration of ultrasound guided axillary brachial plexus block. We hypothesised that using a 20 ml mixture of lidocaine 2% plus epinephrine 1:200,000 combined with clonidine 1 µg/kg will shorten the onset time of sensory block when compared to lidocaine 2% plus epinephrine 1:200,000 in ultrasound guided axillary brachial plexus block (USgABPB) for upper limb trauma surgery.

5.3 Methods

This prospective, randomised, single centre study was approved by The Clinical Research Ethics Committee of Cork Teaching Hospitals [ECM 4(aa) 04/03/14, Chairperson Professor Michael G Molloy], registered at https://clinicaltrials.gov (NCT03207022), and carried out at Cork University Hospital. Written informed consent was obtained from all eligible participants. Twenty-four patients aged 18 or older, ASA grade I-III, undergoing unilateral upper limb surgeries of forearm and hand, were recruited to the study. Exclusion criteria were contraindication to regional anaesthesia, hypersensitivity to amide local anaesthetics or clonidine, intolerance or contraindication to non-steroidal anti-inflammatory drugs, BMI > 35, pregnancy, cardiac conduction abnormalities, history of hepatic or renal failure, and neurological or neuromuscular disease.

On arrival to the anaesthesia induction room, an intravenous cannula was placed in the forearm contralateral to the surgical site, and standard monitors were applied. Using computer-generated sequence of random numbers and a sealed envelope technique, patients were randomised to one of two groups to receive USgABPB with 20 mL of lidocaine 2% plus 1:200,000 epinephrine combined with either 2 mL of normal saline 0.9% (Group 1) or 2 mL of an admixture of clonidine 1 µg/kg and normal saline 0.9% (Group 2). Patients were not made aware of group allocation. All the blocks were performed by an experienced anaesthesiologist skilled in USgABPB. The patients were positioned supine with the operative arm abducted and externally rotated with the elbow flexed at 90˚. Under aseptic precautions the axillary brachial plexus block was performed under ultrasound guidance alone using a SonoSite Titan unit (SonoSite®, Bothwell, WA) with a 38 mm linear array 5–10 MHz transducer

(L38). All four terminal branches, the median, ulnar, radial, and musculocutaneous nerves were identified in the axillary region. A 24-gauge, 50 mm, insulated short bevel needle (Stimuplex® B. Braun, Melsungen, Germany) was advanced in-plane until the needle tip was placed adjacent to the nerve before the local anaesthetic was injected to produce a circumferential spread around each target nerve. The total volume of the local anaesthetic solution corresponding to the study group was equally distributed among the four nerves.

Sensory and motor blockade was evaluated after completion of the injection by an independent observer not aware of group allocation. Assessment of sensory and motor block onset in the innervation area of each nerve (median, ulnar, radial, and musculocutaneous nerve) were carried out every 2.5 mins until surgical anaesthesia was achieved or 30 mins have elapsed. Sensory function was scored as being present or absent and motor function was graded using the modified Bromage Scale (Table 1). Surgical anaesthesia was defined as a motor score ≤2, with absent sensation to cold (tested with ethyl chloride BP, Cryogesic®, Dr Georg Friedrich Henning, Chemische Fabrik Walldorf GmbH, Walldorf, Germany). Each nerve distribution area was individually assessed, and the sensory and motor onset time was measured separately from conclusion of the block (removal of block needle, T_0) to attainment of absent sensation to cold and a motor score ≤2, respectively. Overall sensory and motor block onset time was taken from T_0 to attainment of surgical anaesthesia in all innervation territories. If surgical anaesthesia had not been achieved at 30 mins in one or more of the four nerve distribution areas, a rescue block or general anaesthesia was planned. Any patients with discomfort or pain during surgery requiring supplementation of infiltration by surgeons or requiring opiate analgesia were considered block failure and data from these patients was analysed separately.

In case of patient anxiety or upon request, sedation with midazolam to a maximum of 3 mg was provided. All patients received paracetamol 1 g and diclofenac sodium 75 mg iv intraoperatively. Heart rate, blood pressure, peripheral oxygen saturation, and sedation score on a five-point scale (0 = wide awake, 1 = drowsy, 2 = dozing intermittently , 3 = mostly asleep, and 4= only aroused by tactile stimulation) were recorded every 5 min intraoperatively and every 30 min postoperatively until resolution of the block. Hypotension and bradycardia, defined as a 20% fall in blood pressure and heart rate respectively, in relation to pre block baseline value and any episodes of Spo_2 equal or less than 90% associated with sedation requiring oxygen supplementation by venturi mask were noted.

Postoperatively, duration of sensory and motor block of each nerve was evaluated every 15 mins by an independent observer. The time interval was taken from the completion of the block procedure to the return of sensation to cold and motor power (score ≥3) respectively. Postoperative analgesia consisted of regular paracetamol 1 g po 6 hourly, diclofenac 75 mg po 12 hourly and rescue analgesia was offered in the form of oxycodone 10 mg orally 4-6 hourly as required.

The primary outcome was overall onset of sensory block, which was defined as the time elapsed from conclusion of block (T_0) until attainment of sensory block in all four nerve distribution areas. Similarly, overall onset of motor block was defined as the time interval from T_0 to attainment of motor power (score ≤2) in all four nerve distribution areas. Secondary outcome measures included overall onset of motor block, onset of sensory and motor block of individual nerves, overall duration of sensory and motor block, time to first request of postoperative opioid analgesia and incidence of adverse effects perioperatively.

Sample size and statistical analysis

The sample size was calculated based on the onset of sensory block as the primary outcome parameter. Kaabachi et al[13] found a mean onset of sensory block of 9 (SD ± 3) min following an axillary brachial block performed with 30 mL lidocaine 1.5%. The minimum sample size required to have an 80% probability of detecting a 40% decrease in onset time (level of significance 0.05) was 9 patients per group. We recruited 12 patients per group to account for potential dropouts.

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York). The Shapiro-Wilk test was used for normality testing. Continuous, normally distributed data are presented as mean (SD), and non-normally distributed data as median (interquartile range [IQR]). Comparisons between the groups were analysed using the unpaired Student's t test for normally distributed data and nonparametric data with Mann-Whitney U test. Categorical variables were compared between groups using Pearson or Fischer exact test. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

5.4 Results

Twenty-four patients (12 in each group) were recruited to the study from April 2014 to January 2015. All patients completed the study (Fig 1), and none of the patients required rescue block, conversion to general anaesthesia, supplementation by surgeons, or intraoperative opioid analgesia. The patient demographic characteristics were similar between the groups (Table 1). The overall onset of sensory and motor block was significantly shorter in Group 2 compared to Group 1 (Table 2). This was also noted in the individual nerve block onset times with the exception of musculocutaneous motor block. The overall duration of sensory and motor block was significantly longer in Group 2 compared to Group 1 (Table 3). In addition, overall duration of both sensory and motor block of individual nerves were also longer in Group 2. Figure 2 and 3 depicts the primary outcome measure, overall onset of sensory and motor block.

Haemodynamic parameters (Tables-4,5,6) (Figures-4,5,6), peripheral oxygen saturation and sedation score showed no significant differences between the groups. The highest sedation score of 1 was noted in seven patients, four in Group 1 and three in Group 2 during the intraoperative period which corresponded to receiving midazolam for anxiety. There were no systemic adverse events noted in either group. Twelve patients, eight in Group 1 and four in Group 2, requested additional opiate analgesia postoperatively. The median [IQR] time to first request of supplementary analgesia was longer in Group 2 at 318 [303 – 469] min when compared to 209 [166 – 268] min in Group 1 (P = 0.04).

5.5 Discussion

This study demonstrated that adding clonidine to lidocaine with epinephrine for ultrasound guided axillary brachial plexus block resulted in shorter overall onset time and prolonged duration of both sensory and motor block. Our results are similar to previous findings where by clonidine added to local anaesthetics in conventional axillary brachial plexus block, shortened block onset time[5-7] and prolonged duration of anaesthesia and analgesia following conclusion of blocks.[5-9] In contrast to earlier studies, we performed all blocks solely under ultrasound guidance ensuring uniformity in the deposition of local anaesthetic around all four terminal nerves, thus minimising the differences associated with the technique.

The use of lidocaine, a local anaesthetic with moderate duration of action, allowed detection of any effects attributable to clonidine in the postoperative period. The dose of 1 µg/kg of clonidine was chosen based on previous reports.[5,9] Doses of up to 150 µg have been used with minimal side effects.[14,15] In a dose finding study, Bernard et al demonstrated that the addition of clonidine to lidocaine 1% resulted in more pronounced sensory blockade as well as in a dose dependent prolongation of analgesia.[5] They concluded that 30 to 90 µg clonidine improved the quality of nerve block while limiting the side effects. Similarly, Iohom et al[6] demonstrated that addition of clonidine to mepivacaine in axillary brachial plexus block led to decrease in sensory block onset time and increase in duration of anaesthesia and postoperative analgesia. More recently Hrishi et al,[16] found clonidine added to a mixture of bupivacaine and lidocaine to shorten the onset time and prolong the duration of ultrasound guided supraclavicular block. Of note the heterogeneity of nerve stimulation (single or multiple) or dual ultrasound plus nerve stimulation-based

block techniques used, which may have influenced spread of local anaesthetic within the brachial plexus sheath and subsequent block characteristics.

Addition of clonidine to local anaesthetics for brachial plexus block has been found to be efficacious when compared to systemic administration of similar dose in prolonging the duration of block and postoperative analgesia, suggesting a local mechanism of action of clonidine.[17,18] The precise mechanism, however, in which clonidine exerts its action remains speculative. Several theories have been postulated including that clonidine with selective α_2 adrenoreceptor agonist and weak α_1 agonist activity, causes vasoconstriction by postsynaptic adrenoreceptor activation,[19-21] thus prolonging block duration by reducing the vascular absorption of local anaesthetic mixtures. Other studies did not support those results[11,22] and hypothesised that clonidine may have direct effect on nerve fiber conduction, mainly in A alpha and C fibres.[23-25] Despite this observed effect, clonidine alone has been shown to be incapable of producing analgesia when injected into the axillary brachial plexus sheath.[26]

In the present study, all patients received lidocaine with epinephrine, which alone produces marked vasoconstriction. Whether this effect is further enhanced or prolonged by addition of clonidine remains unknown. It is likely that prolongation of local anaesthetic block occurs due to a combination of pharmacokinetic and pharmacodynamic effects on local anaesthetic actions.[27]

Our study is limited by the moderate sample size. As it was not designed to elucidate the mechanism of action of clonidine, the study did not include a systemic clonidine group. The study adds to the body of evidence supporting the use of clonidine as an

adjuvant to local anaesthetics in improving the efficacy and characteristics of peripheral nerve blocks.

5.6 Conclusion

Admixture of clonidine 1μg/kg to lidocaine with epinephrine for ultrasound guided axillary brachial plexus block resulted in faster onset and longer duration of both sensory and motor block, and longer time to first request of postoperative analgesia.

5.7 Tables

Table 1. Patient characteristics

Continuous variables are presented as means (SD), categorical variables as counts

y = years, n=number

	Group 1 (n=12)	**Group 2 (n=12)**	**P Value**
Age, y	41.4 ± 10.6	42.3 ± 8.6	0.82
Sex, M/F, n	7/5	8/4	0.67
BMI, Kg/m^2	25.8 ± 1.8	25.7 ± 2.0	0.98
ASA grade (I/II/III), n	9/3/0	7/5/0	0.39
Duration of surgery, min	63.9 ± 15.9	61.8 ± 15.4	0.74
Site of surgery (forearm, wrist, hand), n	0/10/2	1/6/5	0.19

Table 2. Sensory and motor block onset time

Data are presented in minutes, values are median (interquartile range, Q1-Q3)

	Group 1 (n=12)	**Group 2 (n=12)**	**P Value**
Overall sensory block, min	10 [8.8 – 12.5]	5 [5 – 7.5]	< 0.001
Overall motor block, min	7.5 [6.3 – 7.5]	5 [2.5 – 7.5]	0.001
Radial nerve block, min			
Sensory	10 [7.5 – 11.3]	5 [3.8 – 7.5]	0.002
Motor	5 [5 – 7.5]	3.8 [2.5 – 5]	0.014
Ulnar nerve block, min			
Sensory	7.5 [7.5 – 10]	5 [5 – 6.3]	0.005
Motor	5 [5 – 7.5]	3.75 [2.5 – 5]	0.007
Median nerve block, min			
Sensory	7.5 [5 – 11.25]	5 [5 – 7.5]	0.001
Motor	5 [5 – 7.5]	3.8 [2.5 – 5]	0.005
Musculocutaneous nerve block, min			
Sensory	7.5 [7.5 – 8.8]	5 [5 – 6.8]	0.003
Motor	5 [2.5 – 6.3]	2.5 [2.5 – 5]	0.18

Table 3. Sensory and motor block duration

Data are expressed in minutes, values are median (IQR)

	Group 1 (n=12)	**Group 2 (n=12)**	**P Value**
Overall sensory block, min	168 [148 - 190]	225 [200 - 231]	< 0.001
Overall motor block, min	168 [148 - 186]	225 [208 - 231]	< 0.001
Radial nerve block, min			
Sensory	175 [148 - 192]	225 [200 - 231]	0.001
Motor	180 [151 - 187]	225 [208 - 231]	< 0.001
Ulnar nerve block, min			
Sensory	182 [156 - 192]	227 [200 - 241]	0.002
Motor	178 [148 - 190]	226 [211 - 233]	< 0.001
Median nerve block, min			
Sensory	180 [156 - 190]	230 [200 - 241]	0.001
Motor	176 [156 - 193]	225 [215 - 238]	< 0.001
Musculocutaneous nerve block, min			
Sensory	180 [156 - 195]	233 [215 - 241]	0.001
Motor	168 [156 - 195]	225 [215 - 231]	< 0.001
Values are median [IQR]			

Table 4: Systolic blood pressure changes

Data expressed in mmHg; values are mean (SD)

	Group 1	**Group 2**	**P value**
Baseline	129.3 ± 7.5	131.7 ± 7.6	0.45
5 min	125.6 ± 5.3	126.6 ± 6.8	0.69
10 min	128.1 ± 5.4	128.9 ± 6.4	0.73
15 min	127.3 ± 7.7	131.4 ± 7.8	0.20
20 min	128.2 ± 4.4	129.6 ± 4.8	0.46
25 min	130.2 ± 6.1	131.8 ± 5.9	0.52
30 min	128.8 ± 8.4	130.2 ± 7.9	0.69
35 min	128.2 ± 6.1	130.4 ± 4.4	0.38
40 min	128.6 ± 4.5	131.2 ± 8.9	0.38
45 min	128.6 ± 5.7	132.3 ± 8.3	0.21
50 min	128.7 ± 7.9	125.5 ± 5.7	0.27
55 min	128.6 ± 5.7	132.3 ± 8.3	0.21
60 min	126.4 ± 6.8	130.8 ± 8.5	0.17
90 min	125.9 ± 8.0	129.1 ± 7.7	0.33
120 min	127.1 ± 6.1	130.7 ± 8.6	0.25
150 min	124.5 ± 6.4	126.6 ± 6.9	0.45
180 min	129.9 ± 6.4	132.3 ± 8.4	0.45
210 min	127.4 ± 8.4	128.8 ± 8.6	0.70
240 min	128.6 ± 4.5	131.2 ± 8.9	0.37

Table 5: Diastolic blood pressure changes

Data expressed in mmHg, values are mean (SD)

	Group 1	**Group 2**	**P value**
Baseline	71.2 ± 6.6	71.4 ± 6.2	0.92
5 min	70.6 ± 5.7	73.8 ± 4.5	0.14
10 min	70.8 ± 3.3	72.0 ± 3.5	0.40
15 min	74.1 ± 6.5	72.8 ± 2.4	0.51
20 min	71.8 ± 6.1	69.3 ± 8.0	0.39
25 min	70.8 ± 6.2	71.6 ± 3.0	0.71
30 min	71.2 ± 6.5	71.6 ± 7.2	0.88
35 min	71.0 ± 5.7	70.8 ± 6.3	0.92
40 min	70.1 ± 6.8	71.8 ± 5.5	0.51
45 min	69.7 ± 6.2	70.3 ± 6.2	0.82
50 min	70.8 ± 4.8	69.3 ± 5.9	0.50
55 min	71.2 ± 6.6	71.4 ± 6.2	0.92
60 min	69.3 ± 6.9	70.2 ± 5.3	0.74
90 min	71.0 ± 5.7	70.8 ± 6.3	0.92
120 min	71.8 ± 5.9	72.1 ± 7.5	0.93
150 min	70.5 ± 6.0	71.2 ± 5.5	0.77
180 min	71.0 ± 5.7	70.8 ± 6.3	0.92
210 min	71.4 ± 5.7	70.3 ± 5.8	0.64
240 min	71.4 ± 5.7	73.1 ± 4.1	0.42

Table 6: Heart rate changes

Values are mean (SD)

	Group 1	**Group 2**	**P value**
Baseline	74.5 ± 2.2	73.6 ± 3.8	0.47
5 min	73.6 ± 3.3	73.4 ± 3.0	0.89
10 min	73.9 ± 2.9	72.8 ± 3.4	0.41
15 min	74.4 ± 2.8	73.7 ± 3.1	0.54
20 min	72.8 ± 4.8	70.9 ± 4.6	0.34
25 min	73.9 ± 3.1	72.2 ± 4.1	0.25
30 min	74.4 ± 2.8	73.7 ± 3.1	0.54
35 min	73.6 ± 3.3	73.7 ± 2.6	0.94
40 min	73.1 ± 3.3	73.4 ± 3.2	0.80
45 min	74.2 ± 3.2	73.1 ± 4.9	0.53
50 min	73.3 ± 4.6	72.3 ± 4.6	0.57
55 min	73.4 ± 3.4	72.5 ± 4.7	0.58
60 min	73.6 ± 3.3	73.4 ± 3.0	0.89
90 min	74.5 ± 2.2	73.6 ± 3.8	0.47
120 min	74.5 ± 1.9	73.5 ± 3.9	0.44
150 min	75.1 ± 2.1	74.1 ± 3.6	0.42
180 min	73.7 ± 2.2	73.6 ± 4.3	0.95
210 min	72.9 ± 2.7	73.8 ± 4.1	0.56
240 min	72.8 ± 2.7	73.3 ± 3.8	0.71

5.8 Figures

Figure 1. Consort flow diagram

n = number

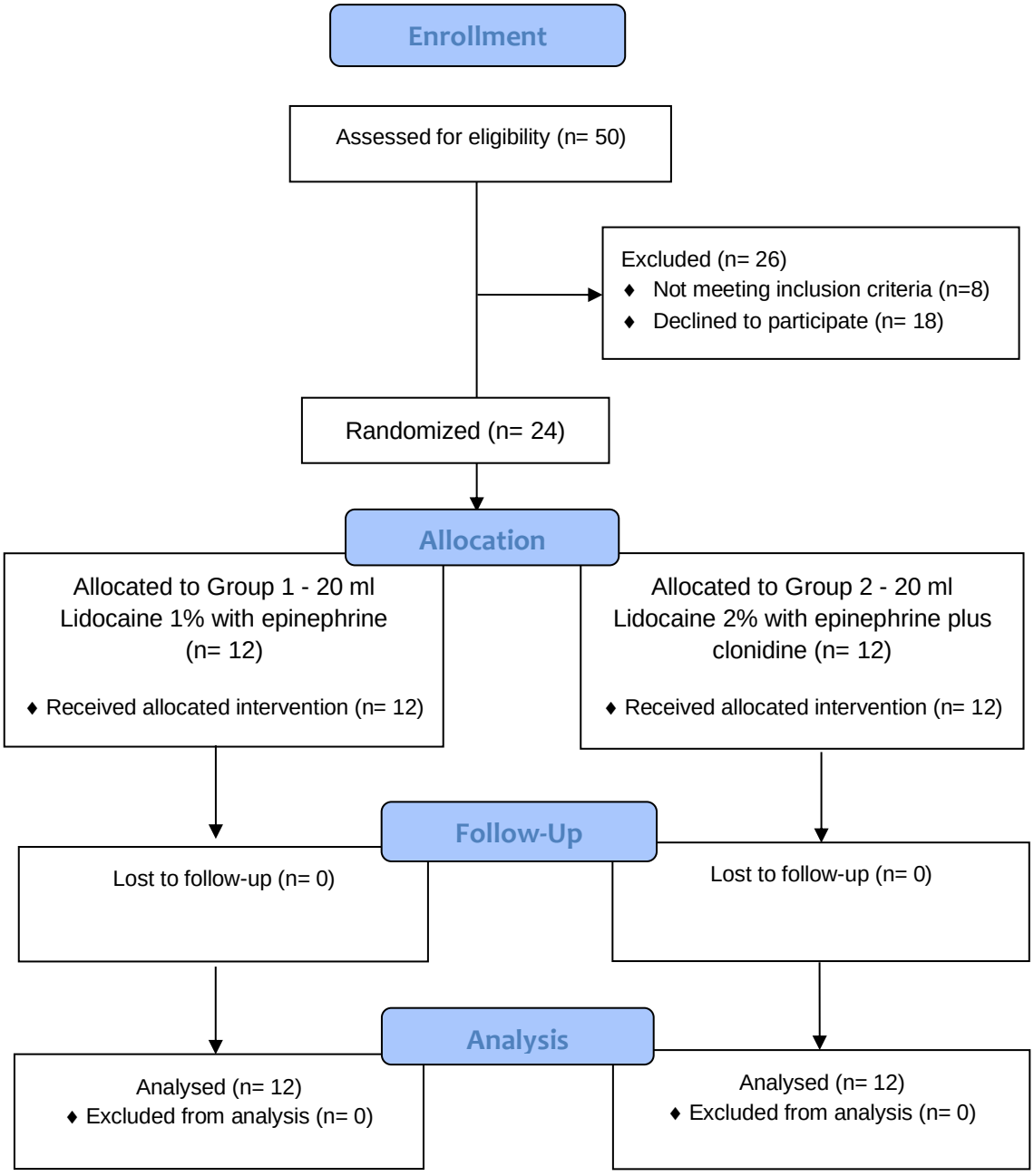


Figure 2. Overall onset of sensory block

The horizontal black line represents the median, the box represents the interquartile range, and the vertical lines show the lowest and highest values.

* P < 0.001

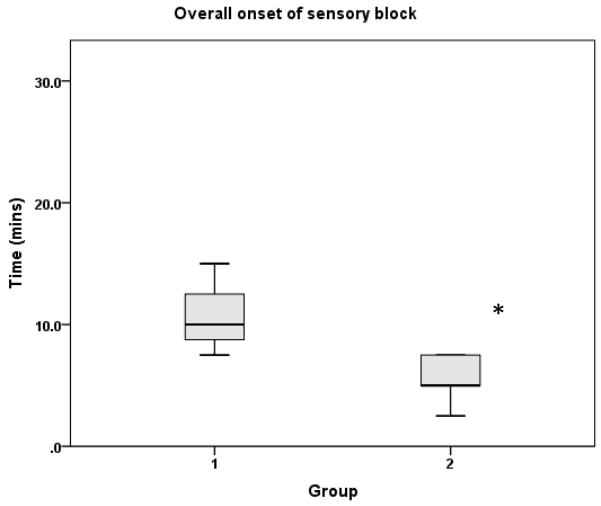


Figure 3. Overall onset of motor block

The horizontal black line represents the median, the box represents the interquartile range, and the vertical lines show the lowest and highest values.

* P = 0.001

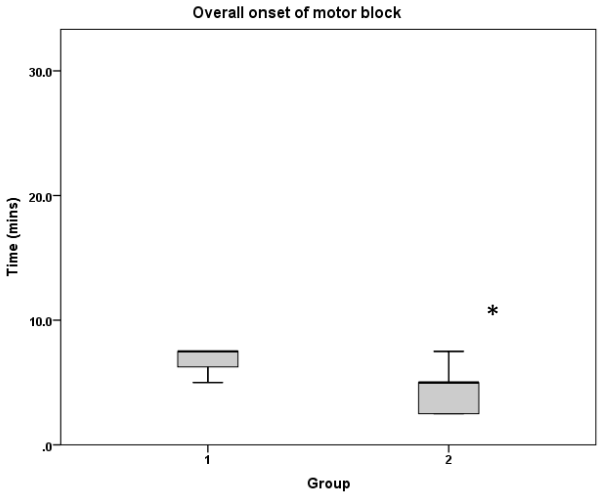


Figure 4. Systolic blood pressure changes (SBP)

The line graphs represent mean and standard deviation in group 1 and 2

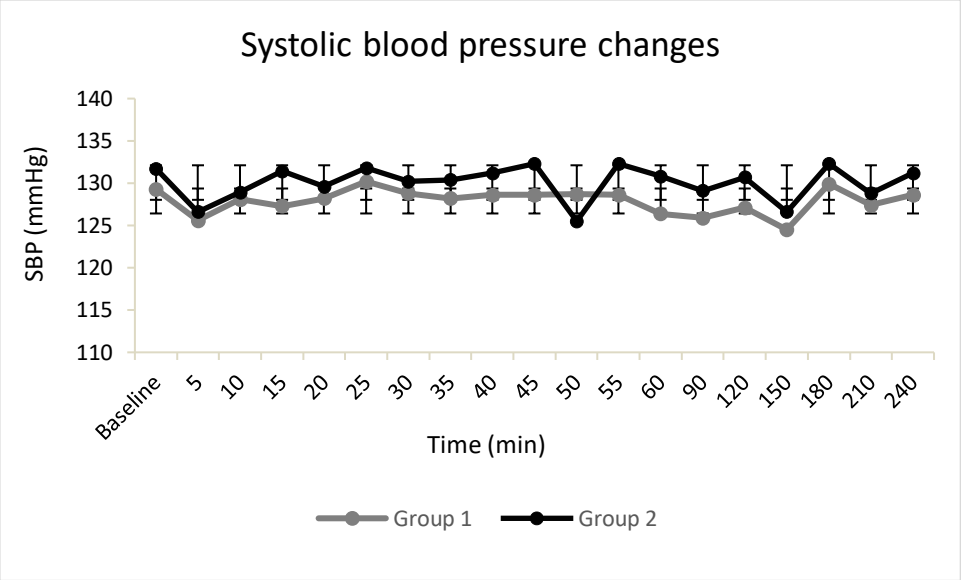


Figure 5. Diastolic blood pressure changes (DBP)

The line graphs represent mean and standard deviation in group 1 and 2

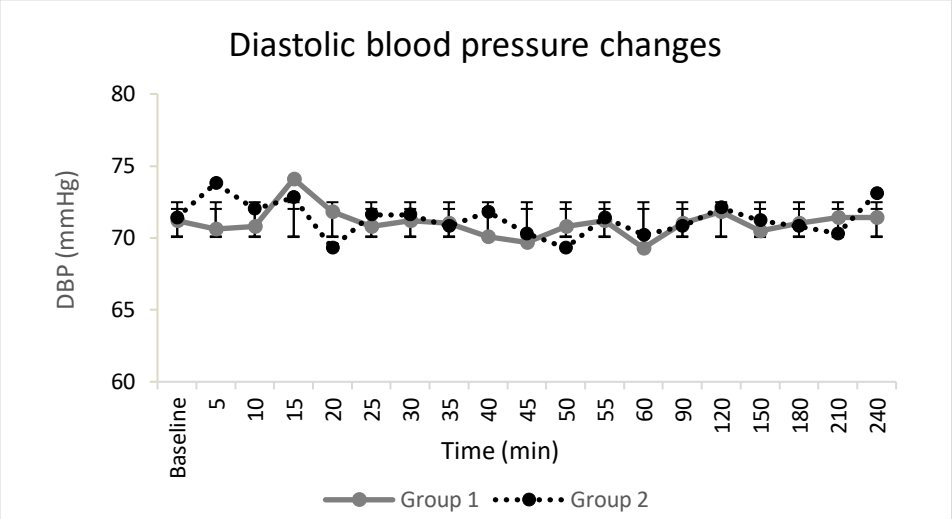
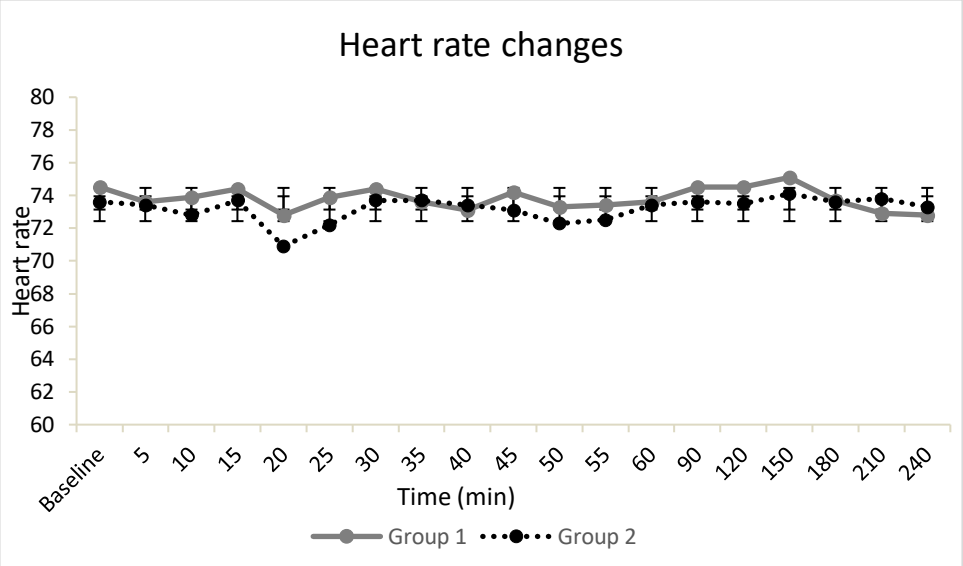


Figure 6. Heart rate changes

The line graphs represent mean and standard deviation in group 1 and 2



5.9 References for chapter 5

1. Bazin JE, Massoni C, Bruelle P, Fenies V, Groslier D, Schoeffler P. The addition of opioids to local anaesthetics in brachial plexus block: the comparative effects of morphine, buprenorphine and sufentanil. *Anaesthesia.* 1997;52(9):858-862.
2. Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD. Buprenorphine added to the local anesthetic for axillary brachial plexus block prolongs postoperative analgesia. *Regional anesthesia and pain medicine.* 2002;27(2):162-167.
3. Dogru K, Duygulu F, Yildiz K, Kotanoglu MS, Madenoglu H, Boyaci A. Hemodynamic and blockade effects of high/low epinephrine doses during axillary brachial plexus blockade with lidocaine 1.5%: A randomized, double-blinded study. *Regional anesthesia and pain medicine.* 2003;28(5):401-405.
4. Iskandar H, Guillaume E, Dixmérias F, et al. The enhancement of sensory blockade by clonidine selectively added to mepivacaine after midhumeral block. *Anesthesia and analgesia.* 2001;93(3):771-775.
5. Bernard JM, Macaire P. Dose-range effects of clonidine added to lidocaine for brachial plexus block. *Anesthesiology.* 1997;87(2):277-284.
6. Iohom G, Machmachi A, Diarra DP, et al. The effects of clonidine added to mepivacaine for paronychia surgery under axillary brachial plexus block. *Anesthesia and analgesia.* 2005;100(4):1179-1183.
7. Antonucci S. [Adiuvants in the axillary brachial plexus blockade. Comparison between clonidine, sufentanil and tramadol]. *Minerva Anestesiol.* 2001;67(1-2):23-27.

8. Erlacher W, Schuschnig C, Koinig H, et al. Clonidine as adjuvant for mepivacaine, ropivacaine and bupivacaine in axillary, perivascular brachial plexus block. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* 2001;48(6):522-525.

9. Singelyn FJ, Gouverneur JM, Robert A. A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. *Anesthesia and analgesia.* 1996;83(5):1046-1050.

10. Eledjam JJ, Deschodt J, Viel EJ, et al. Brachial plexus block with bupivacaine: effects of added alpha-adrenergic agonists: comparison between clonidine and epinephrine. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* 1991;38(7):870-875.

11. Gaumann D, Forster A, Griessen M, Habre W, Poinsot O, Della Santa D. Comparison between clonidine and epinephrine admixture to lidocaine in brachial plexus block. *Anesthesia and analgesia.* 1992;75(1):69-74.

12. Erlacher W, Schuschnig C, Orlicek F, Marhofer P, Koinig H, Kapral S. The effects of clonidine on ropivacaine 0.75% in axillary perivascular brachial plexus block. *Acta anaesthesiologica Scandinavica.* 2000;44(1):53-57.

13. Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Ben Abdelaziz A. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. *Anesthesia and analgesia.* 2009;108(1):367-370.

14. Murphy DB, McCartney CJ, Chan VW. Novel analgesic adjuncts for brachial plexus block: a systematic review. *Anesthesia and analgesia.* 2000;90(5):1122-1128.

15. McCartney CJ, Duggan E, Apatu E. Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Regional anesthesia and pain medicine.* 2007;32(4):330-338.

16. Hrishi AP, Rao G, Lionel KR. Efficacy of Clonidine as an Additive on the Duration of Action of Brachial Plexus Block Performed Under Ultrasound and Nerve Locator Guidance: A Prospective Randomized Study. *Anesthesia, essays and researches.* 2019;13(1):105-110.

17. Singelyn FJ, Dangoisse M, Bartholomée S, Gouverneur JM. Adding clonidine to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. *Regional anesthesia.* 1992;17(3):148-150.

18. Hutschala D, Mascher H, Schmetterer L, et al. Clonidine added to bupivacaine enhances and prolongs analgesia after brachial plexus block via a local mechanism in healthy volunteers. *European journal of anaesthesiology.* 2004;21(3):198-204.

19. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology.* 1991;74(3):581-605.

20. Matthews WD, Jim KF, Hieble JP, DeMarinis RM. Postsynaptic alpha adrenoceptors on vascular smooth muscle. *Federation proceedings.* 1984;43(14):2923-2928.

21. Langer SZ, Duval N, Massingham R. Pharmacologic and therapeutic significance of alpha-adrenoceptor subtypes. *Journal of cardiovascular pharmacology.* 1985;7 Suppl 8:S1-8.

22. Molnar RR, Davies MJ, Scott DA, Silbert BS, Mooney PH. Comparison of clonidine and epinephrine in lidocaine for cervical plexus block. *Regional anesthesia.* 1997;22(2):137-142.

23. Gaumann DM, Brunet PC, Jirounek P. Clonidine enhances the effects of lidocaine on C-fiber action potential. *Anesthesia and analgesia.* 1992;74(5):719-725.

24. Butterworth JFt, Strichartz GR. The alpha 2-adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers. *Anesthesia and analgesia.* 1993;76(2):295-301.

25. Kroin JS, Buvanendran A, Beck DR, Topic JE, Watts DE, Tuman KJ. Clonidine prolongation of lidocaine analgesia after sciatic nerve block in rats Is mediated via the hyperpolarization-activated cation current, not by alpha-adrenoreceptors. *Anesthesiology.* 2004;101(2):488-494.

26. Sia S, Lepri A. Clonidine administered as an axillary block does not affect postoperative pain when given as the sole analgesic. *Anesthesia and analgesia.* 1999;88(5):1109-1112.

27. Kopacz DJ, Bernards CM. Effect of clonidine on lidocaine clearance in vivo: a microdialysis study in humans. *Anesthesiology.* 2001;95(6):1371-1376.

Chapter 6

Conclusions

6.1 Summary of principal findings

Our studies evaluated the effect of local anaesthetic volumes, volume/concentration ratio (dose) and addition of adjuvants on the characteristics of the ultrasound-guided axillary brachial plexus block for upper limb trauma surgeries.

In the first study, **Effect of lidocaine volume on the duration of axillary brachial plexus block: a randomised controlled trial,** we investigated the effect of two volumes (10 vs 30 mL) of lidocaine with epinephrine 1:200 000 on ultrasound-guided axillary brachial plexus block. We observed that using a lesser volume (10ml) when compared to a greater volume (30ml) resulted in shorter overall duration of sensory and motor block, a shorter time to first postoperative analgesia request, and a longer sensory and motor block onset time. There were no block failures, or any adverse events noted in either group.

In the second study, **Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled study,** we examined whether two different volumes and concentrations of a fixed dose of lidocaine with epinephrine by dilution influenced the characteristics of ultrasound guided brachial plexus block. We found that compared to 20 mL of lidocaine 2% with epinephrine, 40 mL of lidocaine 1% with epinephrine resulted in faster overall onset and shorter duration of surgical anaesthesia with significantly better block parameters.

In the third study, **Effects of adding clonidine as an adjuvant to lidocaine with epinephrine for ultrasound guided axillary brachial plexus block: a randomised controlled trial**, we evaluated the effects of adding clonidine 1 µg/kg to 20 mL of

lidocaine 2% with epinephrine 1:200 000 on the onset and duration of sensory and motor block following ultrasound guided axillary brachial plexus block. We observed that admixture of clonidine 1µg/kg to lidocaine with epinephrine block resulted in faster onset and longer duration of both sensory and motor block, and in longer time to first request of postoperative analgesia. There were no systemic adverse events noted with the administered dose of 1µg/kg clonidine.

In addition to this following original body of work a review article was published on **Ultrasound guided axillary brachial plexus block.**

6.2 Clinical implications and future directions

As more surgical procedures are performed on an outpatient basis, often challenged by an ageing population with significant cardiorespiratory disease in high-volume ambulatory centres, regional anaesthesia offers significant benefits in terms of early postoperative pain control and superior recovery profiles.[1-3]

Ultrasound-guided axillary brachial plexus block is an effective, reliable, and most commonly performed technique in providing surgical anaesthesia for patients undergoing forearm and hand surgeries.[2,3] Advances in ultrasound technique have greatly improved the quality and consistency of peripheral nerve block (PNB) achieved .[4] However, one of the limitation of regional anaesthesia is finite duration of the single injection technique. This depends on the type, dose, volume, and concentration of the injected local anaesthetic.

The manner in which these factors influence the clinical effectiveness of the PNB is debatable.[5] There has been heterogeneity in the evidence evaluating the relationship between the dose, volume and concentration of local anaesthetic affecting the reliability, quality and duration of the blockade.[6-23] Analysis of these studies is difficult by virtue of the influence of variables such as:- i. Patient characteristics.[24] ii. Site of administration-variations in their anatomy and neural architecture (non-neural and neural tissue ratio).[25-28] iii. Technique of nerve localisation (nerve stimulation vs ultrasound guidance). iv. Operator dependence.

Variations in operator performance might be partly attributed to the fact that, ultrasound guided PNB is more complex, needs motor and cognitive skills which are quite different from alternate techniques. In our studies, the limited number of

operators contributed , we believe, to the uniformity in the performance of the block. Anaesthesiologists experienced in the ultrasound guided axillary brachial plexus block performed the procedure with an endpoint of identifying all four terminal nerves and obtaining circumferential perineural spread of local anaesthetic.

Our results added the following to the optimisation of the characteristics of the ultrasound guided brachial plexus block. i. Higher volume (30mL compared to 10 mL) of lidocaine 2% with epinephrine for ultrasound-guided axillary brachial plexus resulted in longer overall duration of sensory and motor block, a longer time to first postoperative analgesia request, and a shorter sensory and motor block onset time. ii. Dilution of a fixed dose of lidocaine with epinephrine administered as 40 mL of lidocaine 1% (when compared to 20 mL of lidocaine 2%) with epinephrine resulted in resulted in faster overall onset of block. This, however, was at the expense of a shorter duration of surgical anaesthesia following an ultrasound guided axillary brachial plexus block. iii. Admixture of clonidine 1µg/kg to lidocaine with epinephrine for ultrasound guided axillary brachial plexus block resulted in faster onset and longer duration of both sensory and motor block and, in an extended duration of postoperative analgesia.

Previously, variations in the LA volume (dose) have been administered to improve the efficacy of the PNB. However, the possibility of reducing the volume (and dose) of local anaesthetic with advancement in the ultrasound technique is an obvious advantage from a safety perspective (limiting spread to vital structures[6] or reducing the extent of systemic complications associated with inadvertent intravascular injection[29]). Although our lower volume LA study yielded shorter duration of sensory and motor block merely by 12% and 15%, respectively, this may be of little

clinical relevance if the block can cover the surgical duration and early postoperative analgesia. On the contrary, the duration of lower volume group was similar when compared with the duration of block from our other studies (20 ml of lidocaine 2% with epinephrine 1:200,000). It seems that the relation between volume (dose) and duration of the block is not linear and any increase beyond the threshold volume, improvements in the block characteristics becomes less significant.

Effects of a fixed dose of LA diluted to different volume and concentration on the characteristics of PNB should be interpreted with caution in the context of the site of block and technique employed. We have shown that identical LA dose in a greater volume/lower concentration resulted in faster onset time with subsequent shorter duration of ultrasound guided axillary brachial plexus block. This may be advantageous and desirable in clinical settings with high volume ambulatory surgical centres requiring a rapid turnover of cases. Secondly, improved block performance parameters when a higher volume is at the disposal of the operator may be reassuring in terms of safety of the brachial plexus block technique resulting in fewer needle passes.[30] This could be invaluable if it were to be used in academic centres, teaching ultrasound guided PNB to improve learner performance.

The expanding use of adjuvants to increase clinical duration of local anaesthetics has provided practitioners with an alternate to the more complex perineural catheter techniques if and when a greater duration of anaesthesia and post-operative analgesia is desired. Clonidine in the dose range of up to 150 µg have been used with limited side effects.[31] Our study has shown that adding clonidine at a dose of 1µg/kg to LA is not only safe, but also resulted in superior block onset characteristics with extended duration of anaesthesia and postoperative analgesia.

Our findings indicate an optimal approach may comprise low (dose) volume (10 ml of Lidocaine 2% with epinephrine 1:200, 000) with adjuvant (clonidine 1µg/kg) to enhance the characteristics of ultrasound guided axillary brachial plexus block for patients undergoing upper extremity trauma surgeries. Our research findings also indicates that, dilution of this admixture to a greater volume can be utilised to improve the onset of the brachial plexus block and operator performance characteristics. Importantly, the resolution of block in the postoperative period should be anticipated and managed with timely administration of multi modal analgesics in order to minimise or prevent rebound pain.[32,33]

Reports describing the use of the adjuvants such as dexamethasone, dexmedetomidine or a combination of these look promising for extending the duration of analgesia.[34] Further studies are needed to validate if these adjuvants will have an impact when combined with lower volume of local anaesthetics for PNB. In a paradigm shift, research in the field of regional anaesthesia should not only focus on the efficacy of a given technique or pharmacological agent but rather on patient centred outcomes.

6.3 References for chapter 6

1. Horn JL, Swide C, Gaebel BA, Cross RL, Jr. Comparison of efficiency, recovery profile and perioperative costs of regional anaesthesia vs. general anaesthesia for outpatient upper extremity surgery. *European Journal of Anaesthesiology.* 2007;24(6):557-559.
2. Klein SM, Evans H, Nielsen KC, Tucker MS, Warner DS, Steele SM. Peripheral nerve block techniques for ambulatory surgery. *Anesthesia and Analgesia.* 2005;101(6):1663-1676.
3. O'Donnell BD, Ryan H, O'Sullivan O, Iohom G. Ultrasound-guided axillary brachial plexus block with 20 milliliters local anesthetic mixture versus general anesthesia for upper limb trauma surgery: an observer-blinded, prospective, randomized, controlled trial. *Anesthesia and Analgesia.* 2009;109(1):279-283.
4. Choi S, McCartney CJ. Evidence Base for the Use of Ultrasound for Upper Extremity Blocks: 2014 Update. *Regional Anesthesia and Pain Medicine.* 2016;41(2):242-250.
5. Eng HC, Ghosh SM, Chin KJ. Practical use of local anesthetics in regional anesthesia. *Current Opinion in Anaesthesiology.* 2014;27(4):382-387.
6. 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(4):549-556.
7. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. *Anesthesiology.* 2009;111(1):25-29.

8. Harper GK, Stafford MA, Hill DA. Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound guidance: a pilot study. *British Journal of Anaesthesia.* 2010;104(5):633-636.

9. Serradell A, Herrero R, Villanueva JA, Santos JA, Moncho JM, Masdeu J. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. *British Journal of Anaesthesia.* 2003;91(4):519-524.

10. González AP, Bernucci F, Techasuk W, Pham K, Finlayson RJ, Tran DQ. A randomized comparison between 3 combinations of volume and concentration of lidocaine for ultrasound-guided infraclavicular block. *Regional Anesthesia and Pain Medicine.* 2013;38(3):206-211.

11. van Geffen GJ, van den Broek E, Braak GJ, Giele JL, Gielen MJ, Scheffer GJ. A prospective randomised controlled trial of ultrasound guided versus nerve stimulation guided distal sciatic nerve block at the popliteal fossa. *Anaesthesia and Intensive care.* 2009;37(1):32-37.

12. Casati A, Baciarello M, Di Cianni S, et al. Effects of ultrasound guidance on the minimum effective anaesthetic volume required to block the femoral nerve. *British Journal of Anaesthesia.* 2007;98(6):823-827.

13. Casati A, Fanelli G, Aldegheri G, et al. Interscalene brachial plexus anaesthesia with 0.5%, 0.75% or 1% ropivacaine: a double-blind comparison with 2% mepivacaine. *British Journal of Anaesthesia.* 1999;83(6):872-875.

14. Schoenmakers KP, Wegener JT, Stienstra R. Effect of local anesthetic volume (15 vs 40 mL) on the duration of ultrasound-guided single shot

axillary brachial plexus block: a prospective randomized, observer-blinded trial. *Regional Anesthesia and Pain Medicine.* 2012;37(3):242-247.

15. Smith BE, Siggins D. Low volume, high concentration block of the sciatic nerve. *Anaesthesia.* 1988;43(1):8-11.

16. Taboada M, Alvarez J, Cortés J, Rodríguez J, Atanassoff PG. Is a double-injection technique superior to a single injection in posterior subgluteal sciatic nerve block? *Acta Anaesthesiologica Scandinavica.* 2004;48(7):883-887.

17. Cappelleri G, Ambrosoli AL, Turconi S, Gemma M, Ricci EB, Cornaggia G. Effect of local anesthetic dilution on the onset time and duration of double-injection sciatic nerve block: a prospective, randomized, blinded evaluation. *Anesthesia and Analgesia.* 2014;119(2):489-493.

18. Fenten MG, Schoenmakers KP, Heesterbeek PJ, Scheffer GJ, Stienstra R. Effect of local anesthetic concentration, dose and volume on the duration of single-injection ultrasound-guided axillary brachial plexus block with mepivacaine: a randomized controlled trial. *BMC Anesthesiology.* 2015;15:130.

19. Nuñez Aguado D, López Alvarez S, Salamanca Montaña ME, Janeiro Amela M, Fernández Fernández R, Cobian Llamas JM. [Brachial plexus block with levobupivacaine at the humeral canal: comparison of a small volume at high concentration with a large volume at low concentration]. *Revista Espanola de Anestesiologia y reanimacion.* 2005;52(9):529-535.

20. Nader A, Kendall MC, De Oliveira GS, Jr., et al. A dose-ranging study of 0.5% bupivacaine or ropivacaine on the success and duration of the ultrasound-guided, nerve-stimulator-assisted sciatic nerve block: a double-

blind, randomized clinical trial. *Regional Anesthesia and Pain Medicine.* 2013;38(6):492-502.

21. Fredrickson MJ, White R, Danesh-Clough TK. Low-volume ultrasound-guided nerve block provides inferior postoperative analgesia compared to a higher-volume landmark technique. *Regional Anesthesia and Pain Medicine.* 2011;36(4):393-398.

22. Fredrickson MJ, Smith KR, Wong AC. Importance of volume and concentration for ropivacaine interscalene block in preventing recovery room pain and minimizing motor block after shoulder surgery. *Anesthesiology.* 2010;112(6):1374-1381.

23. Fredrickson MJ, Abeysekera A, White R. Randomized study of the effect of local anesthetic volume and concentration on the duration of peripheral nerve blockade. *Regional Anesthesia and Pain Medicine.* 2012;37(5):495-501.

24. Baeriswyl M, Taffé P, Kirkham KR, et al. Comparison of peripheral nerve blockade characteristics between non-diabetic patients and patients suffering from diabetic neuropathy: a prospective cohort study. *Anaesthesia.* 2018;73(9):1110-1117.

25. Loukas M, Tubbs RS, Stewart D. An abnormal variation of the brachial plexus with potential clinical significance. *The West Indian Medical Journal.* 2008;57(4):403-405.

26. Cornish PB, Leaper C. The sheath of the brachial plexus: fact or fiction? *Anesthesiology.* 2006;105(3):563-565.

27. Areeruk P, Karmakar MK, Reina MA, Mok LYH, Sivakumar RK, Sala-Blanch X. High-definition ultrasound imaging defines the paraneural sheath and fascial compartments surrounding the cords of the brachial plexus at the

costoclavicular space and lateral infraclavicular fossa. *Regional Anesthesia and Pain Medicine.* 2021;46(6):500-506.

28. Moayeri N, Bigeleisen PE, Groen GJ. Quantitative architecture of the brachial plexus and surrounding compartments, and their possible significance for plexus blocks. *Anesthesiology.* 2008;108(2):299-304.

29. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. *Regional Anesthesia and Pain Medicine.* 2013;38(4):289-299.

30. Albrecht E, Chin KJ. Advances in regional anaesthesia and acute pain management: a narrative review. *Anaesthesia.* 2020;75 Suppl 1:e101-e110.

31. McCartney CJ, Duggan E, Apatu E. Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Regional Anesthesia and Pain Medicine.* 2007;32(4):330-338.

32. Sunderland S, Yarnold CH, Head SJ, et al. Regional Versus General Anesthesia and the Incidence of Unplanned Health Care Resource Utilization for Postoperative Pain After Wrist Fracture Surgery: Results From a Retrospective Quality Improvement Project. *Regional Anesthesia and Pain Medicine.* 2016;41(1):22-27.

33. Lavand'homme P. Rebound pain after regional anesthesia in the ambulatory patient. *Current Opinion in Anaesthesiology.* 2018;31(6):679-684.

34. Kang RA, Jeong JS, Yoo JC, et al. Improvement in postoperative pain control by combined use of intravenous dexamethasone with intravenous dexmedetomidine after interscalene brachial plexus block for arthroscopic shoulder surgery: A randomised controlled trial. *European Journal of Anaesthesiology.* 2019;36(5):360-368.

Appendices

Appendix I. Publications: Original/proof of articles

Ultrasound Guided Axillary Brachial Plexus Block

Continuing education

Med Ultrason 2014, Vol. 16, no. 3, 246-251
DOI: 10.11152/mu.2013.2066.163.2kks

Ultrasound guided axillary brachial plexus block

Anil Ranganath, Karthikeyan Kallidaikurichi Srinivasan, Gabriella Iohom

Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital and University College Cork, Wilton, Cork, Ireland

Abstract

The axillary brachial plexus block is the most widely performed upper limb block. It is relatively simple to perform and one of the safest approaches to brachial plexus block. With the advent of ultrasound technology, there is a marked improvement in the success rate of the axillary block. This review will focus on the technique of ultrasound guided axillary brachial plexus block.

Keywords: axillary brachial plexus block, regional anaesthesia, ultrasound

Introduction

Peripheral nerve blocks have seen a big resurgence of interest in the past decade especially with the advent of ultrasound. Nerve blocks have evolved from being an art that only a few physicians can master to more objective and transferable skill largely due to the introduction of ultrasound guidance. Peripheral nerve blocks today are a major component of perioperative multimodal analgesia [1,2]. In particular, for upper extremity surgeries, blocks of brachial plexus (interscalene, supraclavicular, infraclavicular and axillary approaches) have been consistently shown to be associated with time-efficient anaesthesia, faster recovery, fewer adverse events, better analgesia, and greater patient acceptance [3-5].

The axillary brachial plexus block (ABPB) provides surgical anaesthesia at and below the elbow. The technique is relatively simple to perform because of superficial location and relatively lower risk of complications as compared to interscalene (e.g., phrenic nerve block, spinal cord or vertebral artery puncture) or supraclavicular (e.g., pneumothorax) approaches. Inadvertent intraneural and intravascular injections are the only significant risks. Various methods of ABPB have been described such as paraesthesia-seeking, nerve-stimulating, perivascular, trans-arterial, and ultrasound-guided techniques. This review will focus on the ultrasound guided axillary brachial plexus block.

Received 10.06.2014 Accepted 26.03.2014
Med Ultrason
2014, Vol. 16, No 3, 246-251
Corresponding author: Gabriella Iohom MD, PhD
Department of Anaesthesia and Intensive Care Medicine,
Cork University Hospital and University College Cork
Wilton Road, Cork, Ireland.
Phone: +353 21 4922135
Fax: +353 21 4546434
E-mail: gabriella.iohom@hse.ie

Anatomy

The brachial plexus is derived from the ventral rami of C5-8 and T1 nerve roots in most individuals. Occasionally contribution from C4 and T2 nerve roots create a 'prefixed' or 'postfixed' plexus [6]. The roots emerge from the intervertebral foramina and continue between scalenus anterior and medius muscles. Here roots unite to form trunks (upper, middle and lower) and pass downward over the posterior neck triangle and the first rib. At the lateral border of the first rib, behind the clavicle, the trunk divides into divisions (anterior and posterior). These divisions continue into the axilla and form the cords. The anterior divisions of the upper and middle trunks unite to form the lateral cord, while the anterior division of the

lower trunk continues as the medial cord. All three posterior divisions unite to form the posterior cord. These cords are named according to their position around the axillary artery. Each cord ends near the lower border of the pectoralis minor muscle by dividing into two terminal branches. The lateral cord gives off the lateral branch of median nerve and terminates as musculocutaneous nerve. The medial cord gives off the medial branch of median nerve and terminates as ulnar nerve and the posterior cord gives off the axillary nerve and terminates as radial nerve. All these terminal nerves along with the medial cutaneous nerve of arm, forearm and intercostobrachial nerve provide the sensory and motor supply of the upper extremity. The cords, the terminal branches and the vessels lie within an incomplete fascial sheath derived from the prevertebral fascial layer [7].

At the level of axilla, the median, ulnar and radial nerves lie within the neurovascular bundle. The musculocutaneous nerve lies outside the sheath in the plane between the biceps and coracobrachialis muscle, as it leaves the lateral cord before the cords enter the axilla. Within the fascia, in relation to the axillary artery, the nerves are arranged as follows: (1) median-lateral and anterior, (2) ulnar-medial and anterior, and (3) radial-medial and posterior. The musculocutaneous nerve appears lateral and posterior to the artery.

Principles of brachial plexus block

The brachial plexus can be blocked at its various anatomical divisions from nerve roots to its individual terminal branches. The choice of approach depends upon the sensory and motor innervations of the surgical site. The interscalane approach blocks the plexus at the level of roots, thus it is used for shoulder and proximal humerus procedures. The supraclavicular approach blocks the plexus at the level of trunks and divisions providing the most widespread surgical anaesthesia for the whole arm. The infraclavicular approach blocks the cords, whereas the axillary approach blocks the terminal branches thus providing surgical anaesthesia for the elbow, forearm and hand. In addition, the axillary block also provides cutaneous anaesthesia for the inner upper arm which is suitable for procedures requiring tourniquet. Overall, the axillary approach is considered the safest approach because of the lowest risk of serious complications.

Ultrasound guided axillary brachial plexus block

Abramowitz and Cohen described in 1981 the use of Doppler ultrasound to identify the axillary artery, an essential landmark during a difficult perform ABPB [8]. It was, however, the use of B-mode ultrasound in 1989 for axillary block performance that paved the way for ultrasound-guided peripheral nerve blocks [9]. Ultrasound guidance is ideally suited for ABPB for a variety of reasons. The nerves are superficial and therefore easier to identify. The shallow depth of the nerve means that the needle for in-plane approach will be almost perpendicular to the direction of the ultrasound beam, thereby greatly improving needle visibility, which in turn will allow for accurate needle positioning with minimal needle redirections. The vast anatomical variations in position of vascular and neural structures relevant to axillary block [10] will make ultrasound even more suited when compared to conventional landmark guided approach. As one would expect, ultrasound guidance has shown to reduce block performance time, improve block success rate [11-13], shorten onset time [14,15], reduce vascular puncture [16,17] and achieve a reduction in the volume of local anaesthetic required [18].

Ultrasound anatomy

The patient is made comfortable in supine position with the arm abducted and the elbow flexed to 90 degrees. After skin and probe preparation, a linear 38-mm, high frequency 10-12 MHz transducer is placed in the transverse plane at the lateral border of pectoralis major muscle to obtain the best view of the brachial plexus. Image quality is optimised with selection of appropriate depth (within 1-2 cm), focus range (within 1cm) and gain. The structures of interest are very superficial with the pulsating axillary artery localised within 1 cm (fig 1). Easing the pressure on the transducer often reveals one or more axillary veins which is often located medially to the artery (fig 2, fig 3). Surrounding the axillary artery, one will find the three out of four terminal branches of the brachial plexus: the median (superficial and lateral to the artery), the ulnar (superficial and medial to the artery) and the radial (posterior and lateral or medial to the artery) nerves. They often have honey comb appearance with heterogeneous echogenecity. The fourth terminal branch, the musculocutaneous nerve is often seen as a hyperechoic flattened oval shape nerve in the plane between the biceps and coracobrachialis muscles. There is a considerable variation in the position of the nerves among individuals. The median nerve is most commonly seen at 11-12 o'clock position, the ulnar nerve at 2-3 o'clock, the radial nerve at 4-6 o'clock and the musculocutaneous commonly seen at 8-9 at o'clock in relation to the artery [19].

Moving the transducer proximally towards the axilla and distally towards the elbow allows appreciation of the

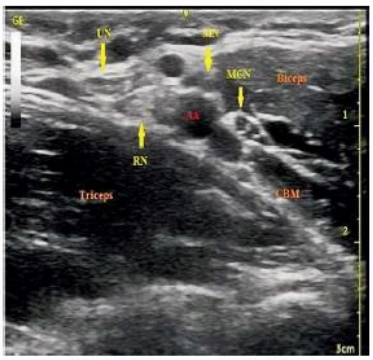


Fig 1. Ultrasound scout scan of axilla showing AA: axillary artery, UN: ulnar nerve, RN: radial nerve, MCN: musculocutaneous nerve and CBM: coracobrachialis muscle

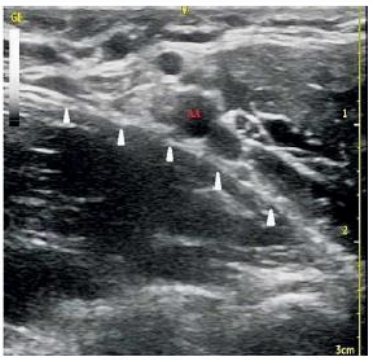


Fig 4. Arrow heads showing sonographic appearance of the conjoint tendon of the latissimus dorsi and teres major muscles

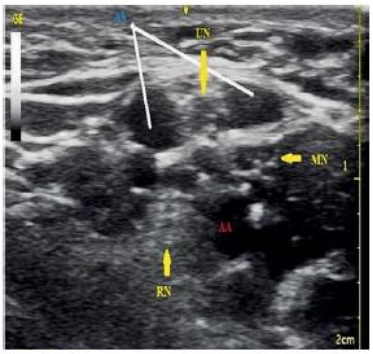


Fig 2. Ultrasound scout scan of axilla showing AV: axillary vein(s). UN: ulnar nerve, MN: median nerve, RN: radial nerve, AA: axillary artery

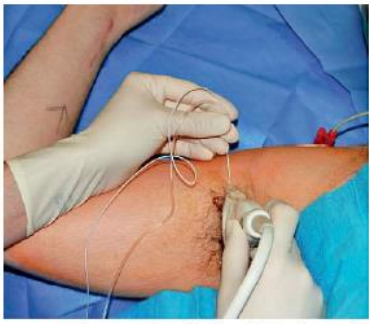


Fig 5. Ultrasound guided axillary brachaial plexus block. In-plane approach of the needle with respect to probe. Also note the position of the patient's upper limb.

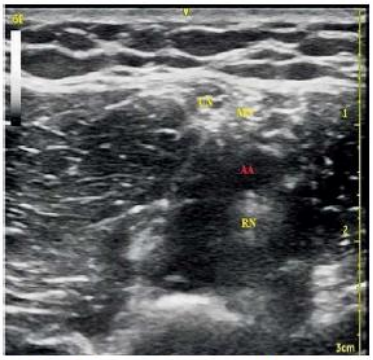


Fig 3. Axillary veins compressed by ultrasound probe

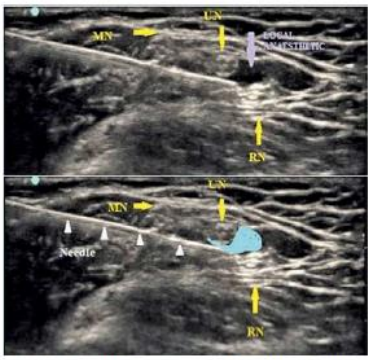


Fig 6. Needle trajectory and local anaesthetic spread around the ulnar nerve (shaded area)

course of each nerve. Of all the nerve, the radial nerve is often difficult to visualise and block. It is important to exclude the post cystic enhancement artefact beneath the artery. Identification of the confluence of the tendons of the latissimus dorsi and teres major with ultrasound may improve the chance of visualising the radial nerve (fig 4). It lies directly anterior to the humeral insertions of the tendons, with anatomic variation of this relation quite uncommon [20].

Needle insertion

In plane approach

A short-bevelled 5 cm 22G insulated needle is inserted parallel to the long axis of the transducer from the lateral side (fig 5). As the needle is in the same plane as an ultrasound beam, the path of the advancement can be visualised in real time as the needle approaches the target nerves (fig 6, fig 7). Ideally, the radial nerve should be targeted first, as it lies posterior to artery, in order to prevent displacing the structures of interest to deeper and obscuring the median and ulnar nerves. The musculocutaneous nerve should be blocked separately outside the neurovascular bundle.

Out of plane approach

The needle insertion is at the short axis of the probe (fig 8). Constant injection of small quantity of injectate is necessary in order to identify the position of the tip of the needle. In terms of safety, in-plane approach offers better visualisation of the needle.

Importantly, a routine of identifying the axillary veins using colour Doppler (fig 9) as they can be easily compressed with the transducer, and visualising the injectate is paramount. Frequent aspiration, slow administration of 1-2 mLs of local anaesthetic and visualisation of the spread of injectate around the nerve is critical to reduce the risks of intravascular or intraneural injection and to increase success rate.

Choice and volume of local anaesthetic solution

This is determined by the desired duration of sensory analgesia. Lidocaine 1.5-2% or mepivacaine 1-1.5% with epinephrine 1:200000 provides effective blockade for 2.5-3 hours. A longer duration may be achieved with use of ropivacaine 0.5% or levobupivacaine 0.5% [21]. Traditionally, greater volumes of local anaesthetic have been administered to achieve successful axillary brachial plexus block [22,23], but recent studies have demonstrated that this can be achieved with even very low volumes of 2-4 mL lidocaine 1.5% per nerve [18] or ultra low volume of 1 mL lidocaine 2% per nerve [24]. However,

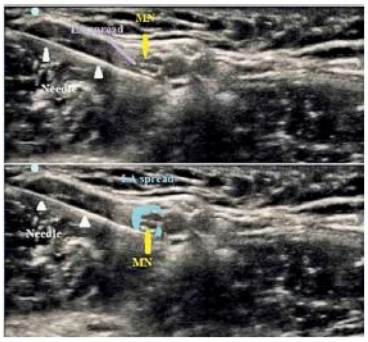


Fig 7. Needle trajectory and local anaesthetic spread around the median nerve (shaded area)

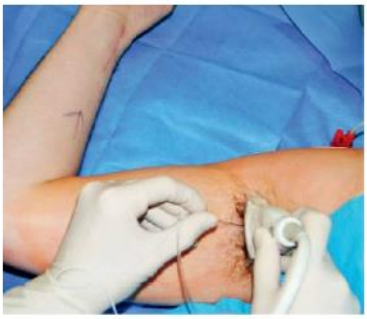


Fig 8. Ultrasound guided axillary brachial plexus block. Out-of-plane approach of the needle with respect to probe.

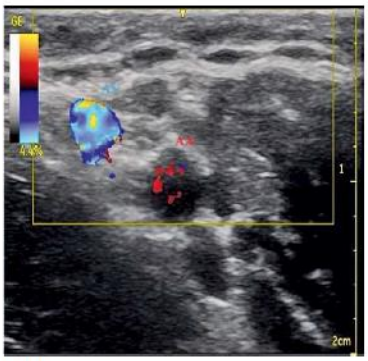


Fig 9. Doppler identification of vessels during ultrasound guided brachial plexus block.

these volumes were believed to be operator dependent. It is recommended to use at least 4-5 mL of local anaesthetic solution for each nerve to achieve successful axillary brachial plexus block.

Perivascular vs perineural

Ultrasound guidance in the performance of axillary block can be applied to

i. perineural injection as described earlier, where the operator identifies and blocks the individual nerves, or
ii. perivascular technique, where the operator blocks the musculocutaneous nerve separately and deposits local anaesthetic solution around the axillary artery, which is in turn believed to achieve blockade of medial, ulnar and radial nerves [25,26].

Both these techniques have been compared by Bernucci et al [27] and found to have similar success rates. However, the latter runs the risk of impaling nerves in inexperienced hands.

Conclusions

Axillary brachial plexus block is effective and widely used technique for providing surgical anesthesia at and below the elbow. It is relatively simple and safe among the four approaches to brachial plexus. With the advent of ultrasound technology, there is a marked improvement in the success rate, shorter onset time and reduction in the volume required for successful block. Paramount importance should be given to continuous visualisation of the needle advancement, tip position and spread of injectate in order to minimise intravascular and intraneural injection.

Conflict of interest: none

References

1. Gritsenko K, Khelemsky Y, Kaye AD, Vadivelu N, Urman RD. Multimodal therapy in perioperative analgesia. Best Pract Res Clin Anaesthesiol 2014; 28: 59-79.
2. Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg 2005; 101: 1634-1642.
3. Hadzic A, Arliss J, Kerimoglu B, et al. A comparison of infraclavicular nerve block versus general anesthesia for hand and wrist day-case surgeries. Anesthesiology 2004; 101: 127-132.
4. Lehmann LJ, Loosen G, Weiss C, Schmittner MD. Interscalene plexus block versus general anaesthesia for shoulder surgery: a randomized controlled study. Eur J Orthop Surg Traumatol 2014 May 15. DOI 10.1007/s00590-014-1483-3.
5. O'Donnell BD, Ryan H, O'Sullivan O, Iohom G. Ultrasound-guided axillary brachial plexus block with 20 milliliters local anesthetic mixture versus general anesthesia for upper limb trauma surgery: an observer-blinded, prospective, randomized, controlled trial. Anesth Analg 2009; 109: 279-283.
6. Barash PG. Clinical Anesthesia. 6th ed. Lippincott Williams & Wilkins; 2009.
7. Barrett HD, Loughnane F, Finucane B, Shorten G. Peripheral nerve blocks and peri-operative pain relief. 1 ed. Philadelphia USA. Saunders; 2004.
8. Abramowitz HB, Cohen C. Use of Doppler for difficult axillary block. Anesthesiology 1981; 55: 603.
9. Ting PL, Sivagnanaratnam V. Ultrasonographic study of the spread of local anaesthetic during axillary brachial plexus block. Br J Anaesth 1989; 63: 326-329.
10. Ustuner E, Yilmaz A, Ozgencil E, Okten F, Turhan SC. Ultrasound anatomy of the brachial plexus nerves in the neurovascular bundle at the axilla in patients undergoing upper-extremity block anesthesia. Skeletal Radiol 2013; 42: 707-713.
11. Chan VW, Perlas A, McCartney CJ, Brull R, Xu D, Abbas S. Ultrasound guidance improves success rate of axillary brachial plexus block. Can J Anaesth 2007; 54: 176-182.
12. Williams SR, Chouinard P, Arcand G, et al. Ultrasound guidance speeds execution and improves the quality of supraclavicular block. Anesth Analg 2003; 97: 1518-1523.
13. Sites BD, Beach ML, Spence BC, et al. Ultrasound guidance improves the success rate of a perivascular axillary plexus block. Acta Anaesthesiol Scand 2006; 50: 678-684.
14. Kapral S, Greher M, Huber G, et al. Ultrasonographic guidance improves the success rate of interscalene brachial plexus blockade. Reg Anesth Pain Med 2008; 33: 253-258.
15. Marhofer P, Schrogendorfer K, Wallner T, Koinig H, Mayer N, Kapral S. Ultrasonographic guidance reduces the amount of local anesthetic for 3-in-1 blocks. Reg Anesth Pain Med 1998; 23: 584-588.
16. Yuan JM, Yang XH, Fu SK, et al. Ultrasound guidance for brachial plexus block decreases the incidence of complete hemi-diaphragmatic paresis or vascular punctures and improves success rate of brachial plexus nerve block compared with peripheral nerve stimulator in adults. Chin Med J (Engl) 2012; 125: 1811-1816.
17. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med 2013; 38: 289-297.
18. Harper GK, Stafford MA, Hill DA. Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound guidance: a pilot study. Br J Anaesth 2010; 104: 633-636.
19. Christophe JL, Berthier F, Boillot A, et al. Assessment of topographic brachial plexus nerves variations at the axilla using ultrasonography. Br J Anaesth 2009; 103: 606-612.

20. Gray AT. The conjoint tendon of the latissimus dorsi and teres major: an important landmark for ultrasound-guided axillary block. Reg Anesth Pain Med 2009; 34: 179-180.
21. Gonzalez-Suarez S, Pacheco M, Roige J, Puig MM. Comparative study of ropivacaine 0.5% and levobupivacaine 0.33% in axillary brachial plexus block. Re Anesth Pain Med 2009; 34: 414-419.
22. Serradell A, Herrero R, Villanueva JA, Santos JA, Moncho JM, Masdeu J. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. Br J Anaesth 2003; 91: 519-524.
23. Vester-Andersen T, Husum B, Lindeburg T, Borrits L, Gothgen I. Perivascular axillary block IV: blockade following 40, 50 or 60 ml of mepivacaine 1% with adrenaline. Acta Anaesthesiol Scand 1984; 28: 99-105.
24. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesthesiology. 2009; 111: 25-29.
25. Imasogie N, Ganapathy S, Singh S, Armstrong K, Armstrong P. A prospective, randomized, double-blind comparison of ultrasound-guided axillary brachial plexus blocks using 2 versus 4 injections. Anesth Analg 2010; 110: 1222-1226.
26. Tran de QH, Pham K, Dugani S, Finlayson RJ. A prospective, randomized comparison between double-, triple-, and quadruple-injection ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med 2012; 37: 248-253.
27. Bernucci F, Gonzalez AP, Finlayson RJ, Tran de QH. A prospective, randomized comparison between perivascular and perineural ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med 2012; 37: 473-477.

Effect of lidocaine volume on the duration of axillary brachial plexus block: a randomised controlled trial

EJA-D-20-01300

EJA

Eur J Anaesthesiol 2021; **38**:1–5

CORRESPONDENCE

Effect of two volumes (10 and 30 ml) of lidocaine 2% and epinephrine on the duration of axillary brachial plexus block

A randomised controlled trial

AQ1 Anil Ranganath, Jassim Rauf, Karthikeyan K. Srinivasan and Gabriella Iohom

AQ2 From the Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital, Wilton Road, Cork, Ireland

AQ3 AQ4 Correspondence to Dr Gabriella Iohom, Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital, Wilton Road, Cork, Ireland
Tel: +353214922135; fax: +353214643454; e-mail: giohom@ucc.ie.

Editor,

Ultrasound guidance has diminished the volume of perineural injectate required to achieve successful surgical anaesthesia.[1–4] The effect of dose reduction on block duration remains unclear. We hypothesised that a lower volume of lidocaine 2% with epinephrine results in a shorter block duration following ultrasound guided axillary brachial plexus block (USgABPB). To test this, we carried out a prospective, randomised controlled clinical trial comparing block duration following performance of an USgABPB with 10 and 30 ml of lidocaine 2% with epinephrine 1 : 200 000, respectively.

Approved by the Clinical Research Ethics Committee of Cork Teaching Hospitals [ECM 4(j) 02/10/12; 20 September 2012, Chairperson Dr Michael Hyland], registered at https://clinicaltrials.gov (NCT03163472), the study was conducted at Cork University Hospital between November 2012 and August 2013. Having obtained written informed consent from each, ASA I-III patients at least 18 years of age, undergoing operative fixation of fractures distal to the elbow, were recruited (Fig. 1). Exclusion criteria were contraindication to regional anaesthesia or to NSAIDs, BMI more than 35, pregnancy, history of hepatic or renal failure, chronic pain, peripheral neuropathy and psychiatric disorder.

Patients were randomised (1 : 1 ratio, computer generated sequence) to receive an USgABPB with either 10 or 30 ml lidocaine 2% with epinephrine, equally distributed around the median, ulnar, radial and musculocutaneous nerve. Patients and assessors were not made aware of group allocation. Each nerve's sensory and motor deficit was assessed every 5 min following removal of the block needle until surgical anaesthesia was achieved or 30 min had elapsed, and every 15 min postoperatively. Sensory function/cold sensation was scored as being present or absent. Motor function was graded using the modified Bromage Scale (0 = no movement, 1 = flicker of movement, 2 = ability to move against gravity but not against resistance, 3 = reduced power but ability to move against resistance, 4 = full power in the relevant muscle).

Surgical anaesthesia was defined as a motor score of 2 or less, with absent sensation to cold. Sensory and motor onset times were taken from the removal of block needle (T_0) to attainment of surgical anaesthesia, separately for each nerve distribution area, and overall for the brachial plexus. The brachial plexus block was considered a failure and the data were excluded from analysis if surgical anaesthesia had not been achieved at 30 min in one or more of the four nerve distribution areas. In this case, a rescue block or conversion to general anaesthesia was planned. Sedation with midazolam up to 3 mg and/or supplemental analgesia with up to 100 μg fentanyl was at the discretion of the attending anaesthesiologist. Minor analgesics (paracetamol 1 g and diclofenac 75 mg) commenced intra-operatively were prescribed for regular postoperative administration. Rescue analgesia was oxycodone 10 mg orally, as required every 4 to 6 h. Block offset in each individual nerve distribution area was defined as return of sensation to cold and motor power (score ≥ 3).

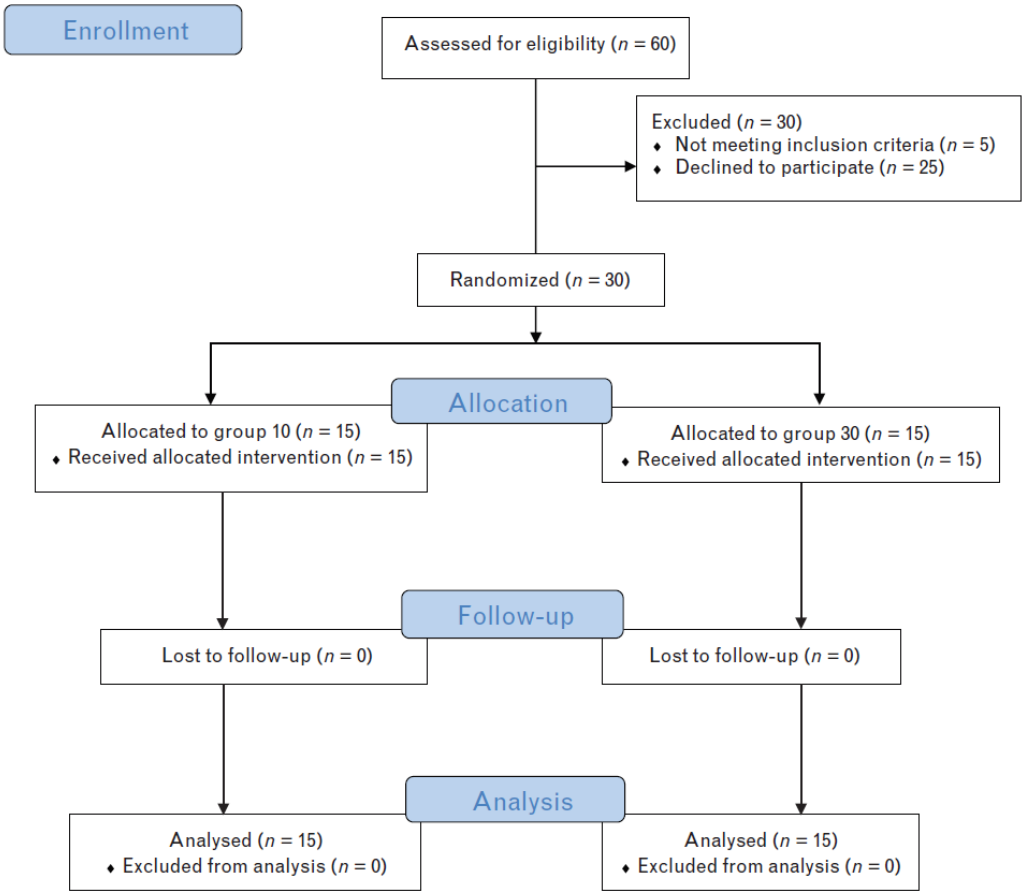
The primary outcome was *overall duration of sensory block*, defined as the time elapsed from T_0 until the return of sensation in any one of the four nerve distribution areas. Similarly, *overall duration of motor block* was defined as the time interval from T_0 to return of motor power (score ≥ 3) in any one nerve distribution area. Secondary outcomes included overall duration of motor block, duration of sensory and motor block of individual nerves, overall and individual block onset times, time to first request of postoperative rescue analgesia and incidence of adverse effects.

On the basis of a historical mean ± SD of 126 ± 48 min[5] with 30 ml lidocaine, a clinically meaningful reduction of 60 min, α risk of 0.05, β risk of 0.01 and a loss to follow-up rate of 10%, 15 patients were required in each group. The Shapiro–Wilk test was used for normality testing. Comparisons between groups were made using the unpaired Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for nonparametric data. Categorical variables were compared between groups using Pearson's or Fischer's exact test. All tests were two-tailed, and *P* value less than 0.05 was considered statistically significant.

Patient characteristics are summarised in Table 1. Overall sensory and motor block onset times were shorter in Group 30 than in Group 10 (Table 2). This was reflected

DOI:10.1097/EJA.0000000000001485

Fig. 1 CONSORT patient flow diagram



n = number.

in the individual nerve onset times with the exception of radial sensory and musculocutaneous motor block. Overall duration of sensory and motor block was 12 and 15% shorter, respectively, in Group 10 (Table 3). In addition, the duration of both sensory and motor block of individual nerves were shorter in Group 10. No rescue block, conversion to general anaesthesia or intra-operative opioid analgesia was required. In Group 10 and 30, three and

Table 1 Baseline demographics and clinical characteristics

	Group 10 ($n = 15$)	Group 30 ($n = 15$)	P
Age (years)	49 ± 15.1	50 ± 22.1	0.91
Sex, M/F, n (proportion)	8/7 (53%/47%)	9/6 (60%/40%)	0.71
BMI (kg m^{-2})	25.7 ± 3.1	27.1 ± 2.9	0.21
ASA grade (I/II/III), n (proportion)	7/7/1 (47%, 47%, 6%)	7/8/0 (47%, 53%)	0.59
Duration of surgery (min)	55.13 ± 19.2	55.33 ± 9.3	0.97
Site of surgery (forearm, wrist, hand), n	0/13/2	1/11/3	

Continuous variables are presented as mean ± SD, categorical variables as counts. n, number; SD, standard deviation; y, years.

Table 2 Sensory and motor block onset time

	Group 10 ($n=15$)	Group 30 ($n=15$)	P
Overall sensory onset	15 [10 to 15]	10 [5 to 15]	0.045
Overall motor onset	10 [10 to 15]	5 [5 to 10]	0.013
Radial			
Sensory onset	15 [10 to 15]	5 [5 to 15]	0.053
Motor onset	10 [5 to 15]	5 [5 to 5]	0.016
Ulnar			
Sensory onset	10 [5 to 15]	5 [5 to 5]	0.012
Motor onset	10 [10 to 15]	5 [5 to 10]	0.005
Median			
Sensory onset	10 [5 to 15]	5 [5 to 10]	0.019
Motor onset	10 [5 to 15]	5 [5 to 5]	0.001
Musculocutaneous			
Sensory onset	10 [5 to 10]	5 [5 to 5]	0.006
Motor onset	10 [5 to 10]	5 [5 to 5]	0.087

Data are presented in min, values are median [IQR]. IQR, interquartile range, the middle 50% of data spread.

Table 3 Sensory and motor block duration

	Group 10 ($n=15$)	Group 30 ($n=15$)	P	Difference,[a] %
Overall sensory duration	165 [142 to 172]	188 [173 to 205	<0.001	12
Overall motor duration	165 [147 to 180]	195 [175 to 220]	0.001	15
Radial nerve				
Sensory duration	165 [147 to 185]	195 [173 to 218]	0.001	15
Motor duration	172 [147 to 185	204 [185 to 225]	0.001	16
Ulnar nerve				
Sensory duration	165 [151 to 185	195 [179 to 220]	0.002	15
Motor duration	166 [152 to 185	205 [188 to 235]	<0.001	19
Median nerve				
Sensory duration	169 [143 to 180]	190 [179 to 220]	<0.001	11
Motor duration	169 [147 to 187]	195 [182 to 235]	0.005	13
Musculocutaneous nerve				
Sensory duration	165 [147 to 185]	195 [185 to 230]	0.002	15
Motor duration	166 [157 to 185]	210 [182 to 235]	0.001	20

Data are expressed in minutes, values are median [IQR]. IQR, interquartile range, the middle 50% of data spread. [a]Difference = difference between the median of Group 30 and Group 10 as a percentage of the median value of Group 30.

four patients received intra-operative sedation for anxiety, and 12 and 8 requested postoperative opiate analgesia, respectively. The median [IQR] time to first request of supplementary analgesia was longer in Group 30 at 267 [224 to 313] min when compared with 188 [168 to 224] min in Group 10 ($P=0.011$). No adverse events were noted.

The most important finding of this study is that a lower volume of lidocaine resulted in shorter overall duration of sensory and motor block and a shorter time to first request of postoperative analgesia. The clinical implication lies with the expected time of dissipation of sensory block, important for both patient expectations management and timing of systemic analgesia aimed at controlling rebound pain.

Few studies evaluated specifically the effect of volume on block duration. Correlation was found between a lower volume of mepivacaine 1.5% and shorter duration of sensory median and ulnar nerve block with no effect on block onset time.[6] Sensory and motor block duration was 17 and 19% shorter, respectively, when using 15 vs. 40 ml mepivacaine 1.5% in USgABPB.[7] Our study, the first to investigate block duration following lidocaine 2%, showed similar outcomes.

Residual block assessments at 15 min intervals may have missed the precise time of resolution thus overestimating block duration. Had we assessed postoperative pain scores, we could have characterised rebound pain. This area deserves further investigation.

In conclusion, using 10 vs. 30 ml lidocaine 2% with epinephrine for USgABPB resulted in shorter overall duration of sensory block following a longer onset time.

Acknowledgements relating to this article

Assistance with this letter: Mr Bahman Honsari provided statistical expertise.

Financial support and sponsorship: departmental.

Conflicts of interest: none.

References

1 Lo N, Brull R, Perlas A, *et al.* Evolution of ultrasound guided axillary brachial plexus blockade: retrospective analysis of 662 blocks. *Can J Anaesth* 2008; **55**:408–413.

2 Abrahams MS, Aziz MF, Fu RF, Horn JL. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; **102**:408–417.
3 Harper GK, Stafford MA, Hill DA. Minimum volume of local anaesthetic required to surround each of the constituent nerves of the axillary brachial plexus, using ultrasound guidance: a pilot study. *Br J Anaesth* 2010; **104**:633–636.
4 O'Donnell B, Riordan J, Ahmad I, Iohom G. Brief reports: a clinical evaluation of block characteristics using one milliliter 2% lidocaine in ultrasound-guided axillary brachial plexus block. *Anesth Analg* 2010; **111**:808–810.
5 Kaabachi O, Ouezini R, Koubaa W, *et al.* Tramadol as an adjuvant to lidocai for axillary brachial plexus block. *Anesth Analg* 2009; **108**:367–370.
6 Ponrouch M, Bouic N, Bringuier S, *et al.* Estimation and pharmacodynar consequences of the minimum effective anesthetic volumes for median a ulnar nerve blocks: a randomized, double-blind, controlled comparison between ultrasound and nerve stimulation guidance. *Anesth Analg* 201 **111**:1059–1064.
7 Schoenmakers KP, Wegener JT, Stienstra R. Effect of local anesthetic volume (15 vs 40 mL) on the duration of ultrasound-guided single shot axillary brachial plexus block: a prospective randomized, observer-blinde trial. *Reg Anesth Pain Med* 2012; **37**:242–247.

Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled study

Ahead of print

Med Ultrason 2021:0, 1-6 Online first
DOI: 10.11152/mu-xxxx

Effects of local anaesthetic dilution on the characteristics of ultrasound guided axillary brachial plexus block: a randomised controlled study

Anil Ranganath, Osman Ahmed, Gabriella Iohom

Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital, Cork, Ireland

Abstract

Aims: Ultrasound guidance has led to marked improvement in the success rate and characteristics of peripheral nerve blocks. However, effects of varying the volume or concentration of a fixed local anaesthetic dose on nerve block remains unclear. The purpose of our study was to evaluate whether at a fixed dose of lidocaine, altering the volume and concentration will have any effect on the onset time of ultrasound-guided axillary brachial plexus block. **Material and methods:** Twenty patients were randomised to receive an ultrasound-guided axillary brachial plexus block with either lidocaine 2% with epinephrine (20 ml, Group 2%) or lidocaine 1% with epinephrine (40 ml, Group 1%). The primary endpoint was block onset time. Secondary outcomes included duration of the block, performance time, number of needle passes, incidence of paraesthesia and vascular puncture. **Results:** The median [IQR] onset time of surgical anaesthesia was shorter in Group 1% when compared to Group 2% (6.25 [5-7.5] min vs 8.75 [7.5-10] min; p=0.03). The mean (SD) overall duration of surgical anaesthesia was significantly shorter in Group 1% compared to Group 2% (150.9±17.2 min vs 165.1±5.9 min; p=0.02). Group 1% had a shorter performance time with fewer needle passes. The incidence of vascular puncture and paraesthesia was similar in the two groups. **Conclusion:** Ultrasound-guided axillary brachial plexus blocks performed using a higher volume of lower concentration lidocaine was associated with shorter onset time and duration of surgical anaesthesia.

Keywords: brachial plexus block; axillary; ultrasound; local anaesthetic; lidocaine

Introduction

Ultrasound-guided axillary brachial plexus block (USgABPB) is an effective and reliable technique for the provision of surgical anaesthesia for forearm and hand surgeries [1-4]. Previously, numerous studies have compared efficacy of brachial plexus block using different local anaesthetic solutions of varying concentrations and volumes [5-7]. However, only few studies have shown that, at constant dose, altering the volume or concentration can affect the characteristics of the nerve block. Historically, it has been reported that higher concentration/lower volume yielded a shorter onset time when compared to higher volume/lower concentration solution using a single injection nerve stimulation technique for sciatic nerve block [8,9]. In contrast, in perivascular axillary blocks with a fixed dose of local anaesthetic, larger volumes provided a better quality sensory [10] and quicker onset motor block [11] when compared to lower volumes. The results from these studies were inconsistent with respect to onset time, success rate and duration of the block. In addition, it is unknown whether they can be replicated with ultrasound guidance. We have chosen to focus on the USgABPB with lidocaine plus epinephrine which is offered preferentially to ambulatory upper limb trauma patients at our institution [12].

In this prospective, randomised, double-blind study, we examined whether two different volumes and concentrations of a fixed dose of lidocaine with epinephrine

Received 02.02.2021 Accepted 05.06.2021
Med Ultrason
2021:0 Online first, 1-6
Corresponding author: Dr Gabriella Iohom PhD
Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital,
Wilton Road, Cork, Ireland
Phone: +353214922135
Fax: +353214643454
E-mail: giohom@ucc.ie

influenced the characteristics of USgABPB. We hypothesised that 40 mL of lidocaine 1% with epinephrine would result in a shorter onset time when compared to 20 mL of lidocaine 2% with epinephrine.

Material and methods

This single centre study was approved by the Clinical Research Ethics Committee of Cork Teaching Hospitals, Cork, Ireland [ECM 4(mm) 01/07/14; 01 July 2014, Chairperson Professor Michael G Molloy], registered at https://clinicaltrials.gov (NCT03207035), and carried out at Cork University Hospital. Having obtained written informed consent from each, patients aged 18 years or older, ASA grade I-III scheduled to undergo minor unilateral upper limb trauma surgery of the hand or forearm, were enrolled in the study. Exclusion criteria were contraindication to regional anaesthesia, hypersensitivity to amide local anaesthetics, intolerance, or contraindication to non-steroidal anti-inflammatory drugs, BMI >35, pregnancy, cardiac conduction abnormalities, history of hepatic and renal impairment, chronic pain, neuromuscular disease, and psychiatric disorder.

Patients were randomised using computer-generated sequence of random numbers and sealed envelope technique, prepared by an investigator with no clinical involvement in the trial. They were subsequently allocated to receive USgABPB with either 20 mL lidocaine 2% with 1:200,000 epinephrine (Group 2%) or 40 mL lidocaine 1% with 1:400,000 epinephrine (Group 1%) (diluted up to the study volume with 0.9% saline). Intravenous access was established in the contralateral upper limb and standard monitoring was employed throughout the procedure. The operative arm was abducted and externally rotated with the elbow flexed at 90°. Under aseptic precautions the axillary brachial plexus block was performed under ultrasound guidance alone using a SonoSite Titan unit (SonoSite®, Bothwell, WA) with a 38 mm linear array 5–10 MHz transducer (L38). Following the identification of the median, ulnar, radial, and musculocutaneous nerves in the axillary region, a 50 mm 24-gauge insulated short bevel needle (Stimuplex® B. Braun, Melsungen, Germany) was advanced in-plane towards each nerve with the aim of surrounding it with either 5 mL (Group 2%) or 10 mL (Group 1%) of local anaesthetic solution. Dynamic manipulation of the needle was sought to facilitate the circumferential perineural spread of local anaesthetic. All blocks were performed by an operator experienced in USgABPB.

Block assessment

Upon completion of the block, a blinded observer not aware of the injectate volume, assessed the onset of sensory and motor block in the innervation area of each nerve (median, ulnar, radial, and musculocutaneous nerve) every 2.5 mins, until surgical anaesthesia was achieved or 30 mins have elapsed. Sensory function was scored as being present or absent and motor function was graded using the modified Bromage scale (Table I) [4]. Surgical anaesthesia was defined as a motor score ≤ 2, with absent sensation to cold (tested with ethyl chloride BP, Criogesic®, Dr Georg Friedrich Henning, Chemische Fabrik Walldorf GmbH, Walldorf, Germany). Each nerve distribution area was individually assessed, and the sensory and motor onset time was measured separately from conclusion of the block (removal of block needle, T_0) to attainment of absent sensation to cold and a motor score ≤ 2, respectively. Overall sensory and motor block onset time was taken from T_0 to attainment of surgical anaesthesia in all innervation territories. The block was considered a failure if surgical anaesthesia had not been achieved at 30 mins in one or more of the four nerve distribution areas. In case of block failure, an additional rescue block or conversion to general anaesthesia was planned together with separate analysis of data from those patients. All patients received paracetamol 1 g and diclofenac sodium 75 mg iv intraoperatively. In case of patient discomfort or upon request, sedation with midazolam to a maximum of 3 mg and/or supplemental analgesia with up to 100 ug fentanyl was provided at the discretion of the attending anaesthesiologist.

Table I. Motor and Sensory Testing

	Motor test	Sensor test
Median nerve	Flexion of radial 3 fingers	Thenar eminence
Radial nerve	Extension of wrist	Dorsum of hand
Ulnar nerve	Abduction of fingers	Hypothenar eminence
Musculocutaneous nerve	Elbow flexion	Over base first metacarpal

Modified Bromage scale [4].

4	Full strength in relevant muscle.
3	Reduced strength but ability to move muscle against resistance
2	Ability to move relevant muscle group against gravity but not against resistance
1	Flicker of movement in relevant muscle group
0	No movement in relevant muscle group

Postoperative analgesia was prescribed around the clock in the form of paracetamol 1 g po 6 hourly and diclofenac 75 mg po 12 hourly. Oxycodone 10 mg orally 4-6 hourly was administered as rescue analgesia. Postoperatively, sensory and motor function of each nerve was assessed every 15 mins. Sensory and motor duration was measured separately for each nerve from T_0 to return of sensation to cold and motor power to ≥3, respectively. Overall sensory and motor block offset was defined as return of sensation to cold and motor power (score ≥3) respectively, in any one nerve distribution area.

The primary outcome was overall surgical anaesthesia onset time, which was defined as the time elapsed from conclusion of block (T_0) until attainment of surgical anaesthesia in all nerves distribution areas. Secondary outcome measures included overall duration of sensory and motor block, as well as sensory and motor onset times and durations of individual blocks. Overall duration of surgical anaesthesia was defined as time elapsed from T_0 to return of sensation and motor power (score ≥3) respectively in any one nerve distribution area.

Block performance parameters were recorded such as *imaging time* (defined as time elapsed from placement of US probe on the patient to acquisition of a satisfactory image of the axillary artery and surrounding nerves) and *needling time* (defined as the time interval between insertion and removal of block needle). Thus, *performance time* was defined as the sum of imaging and needling times. The number of needle passes were recorded. The initial needle pass was considered as the first pass and any subsequent needle advancement preceded by retraction of 1 cm counted as an additional pass. Incidences of vascular puncture and paraesthesia were also noted.

Sample size and statistical analysis

In the absence of data from previous studies using 20 ml of lidocaine 2% with epinephrine for ultrasound guided axillary brachial plexus block, sample size was calculated based on our pilot study of 10 patients. We found a mean ± SD onset time of 11.25±2.3 min. The minimum sample size required to have an 80% probability of detecting a 30% decrease in onset time (level of significance 0.05) was 7 patients per group. We recruited 10 patients per group to account for potential dropouts.

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York). The Shapiro-Wilk test was used for normality testing. Continuous, normally distributed data are presented as mean (SD), and non-normally distributed data as median (interquartile range [IQR]). Comparison between groups were analysed using the unpaired Student's t test for normally distributed data and the Mann-Whitney U test for nonparametric data. Categorical variables were compared between groups using Pearson's or Fischer's exact test. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Twenty patients (10 in each group) were recruited to the study from September 2014 to August 2015. All patients completed the study (fig 1) and none of the patients required rescue block, conversion to general anaesthesia or intraoperative opioid analgesia. There were no adverse events noted in either group. The patient demographic characteristics were similar between the groups (Table II). Table III details onset times. The median [IQR] overall onset time of surgical anaesthesia was shorter in Group 1% compared to Group 2%. The overall onset time of sensory but not motor block was also shorter in Group 1%. Onset times of individual nerves were similar in the two groups, with the exception of median sensory onset time which was shorter in Group 1%. Table IV depicts block durations. The mean (SD) overall duration of surgical anaesthesia was shorter in Group 1% compared to Group 2%, reflective of overall motor block duration. Individual sensory and motor block durations were similar, with median motor block duration shorter in Group 1%. Figure 2 shows the primary outcome measure, overall onset of surgical anaesthesia.

Table II. Patient characteristics

	Group 2% (n=10)	Group 1% (n=10)	p value
Age, y	46.8±18.2	48±15.7	0.88
Sex, M/F, n	7/3	8/2	0.60
BMI, Kg/m^2	25.3±3.2	24.5±3.6	0.62
ASA grade (I/II/III), n	7/3/0	4/6/0	0.18
Duration of surgery, min	62±10.8	58.5±14.9	0.56
Site of surgery (wrist/hand), n	5/5	6/4	

Continuous variables are presented as means ± SD, categorical variables as counts

Group 1% had a shorter needling time, performance time and fewer needle passes when compared to Group 2%. No difference was found between the groups with respect to imaging time, incidence of vascular puncture or paraesthesia (Table V).

Discussion

In this single centre randomised controlled trial, we observed that when using 400 mg of lidocaine with epinephrine, increasing the volume of injectate by dilution

Table III. Sensory and Motor Block Onset Times

	20 ml Lidocaine 2% (n=10)	40 mL Lidocaine 1% (n=10)	p value
Overall sensory onset	8.75 [5-10]	5 [5-7.5]	**0.046**
Overall motor onset	6.25 [5-7.5]	5 [2.5-7.5]	0.41
Overall onset of surgical anaesthesia	8.75 [7.5-10]	6.25 [5-7.5]	**0.03**
Radial			
Sensory	5 [5-10]	5 [2.5-7.5]	0.12
Motor	5 [2.5-7.5]	3.75 [2.5-5]	0.55
Ulnar			
Sensory	6.25 [5-7.5]	5 [2.5-5]	0.12
Motor	5 [2.5-7.5]	5 [2.5-7.5]	0.87
Median			
Sensory	6.25 [5-10]	5 [2.5-5]	**0.03**
Motor	5 [2.5-7.5]	5 [2.5-5]	0.93
Musculocutaneous			
Sensory	5 [5-10]	3.75 [2.5-5]	0.10
Motor	3.75 [2.5-5]	5 [2.5-5]	0.87

Values are Median [IQR] expressed in min

Table IV. Sensory and Motor Block Duration

	Group 2% (n=10)	Group 1% (n=10)	p value
Overall sensory duration	171.6±7.1	158.4±21.7	0.08
Overall motor duration	165.1±5.9	150.9±17.2	**0.02**
Overall duration of surgical anaesthesia	165.1±5.9	150.9±17.2	**0.02**
Radial nerve			
Sensory	176.1±3.7	167.40±20.4	0.20
Motor	170.1±7.2	158.4±18.6	0.08
Ulnar nerve			
Sensory	174.6±3.6	168.9±22.4	0.44
Motor	168.6±8.0	158.4±19.7	0.15
Median nerve			
Sensory	173.1±5.9	162.9±19.9	0.14
Motor	168.1±7.4	152.4±15.4	**0.01**
Musculocutaneous nerve			
Sensory	173.1±7.8	161.4±19.9	0.10
Motor	166.6 ± 7.3	152.4 ± 20.4	0.05

Values are Mean±SD, expressed in min

Table V. Block performance data

	Group 2% (n=10)	Group 1% (n=10)	p value
Imaging time, min (A)	2.5 ± 0.5	2.4 ± 0.6	0.70
Needling time, min (B)	8.5 ± 1.2	6.7 ± 0.9	**0.002**
Performance time, mins (A+B)	10.9 ± 1.3	9.1 ± 0.5	**0.001**
No. needle passes	10.5 ± 2.3	7.2 ± 1.0	**0.001**
Vascular puncture, n (%)	2 (20)	1 (10)	0.53
Paraesthesia, n (%)	4 (40)	2 (20)	0.48

Continuous variables are presented as mean ± SD, categorical variables as count/or percentage.

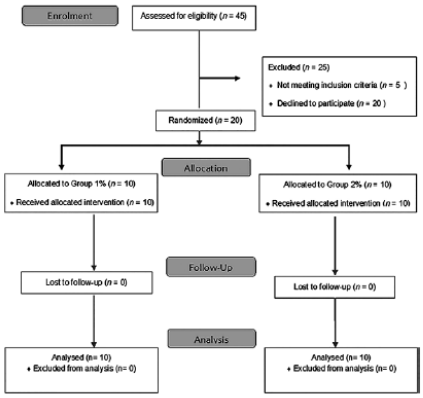


Fig 1. CONSORT patient flow diagram. n = number

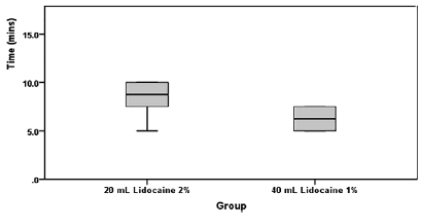


Fig 2. Overall onset of block. The horizontal black line represents the median, the box represents the interquartile range, and the vertical lines show the lowest and highest values. *p = 0.02

resulted in shorter overall onset time and subsequent shorter duration of ultrasound guided axillary brachial plexus block. While the shorter onset may be advantageous and desirable in clinical settings with high volume activity and quick turnover, it appears to come at the expense of a shorter duration of block which should be both anticipated and managed appropriately.

In theory, both concentration and volume of the perineural injectate can influence the characteristics of the nerve block. Higher concentrations may shorten the onset time by facilitating the diffusion of local anaesthetic molecules into the nerve [9], while larger volumes may influence the block onset time by promoting injectate spread around neural structures [11]. However, how the volume/concentration ratio at a fixed local anaesthetic dose affects the characteristics of a nerve block, remains unclear. Previous studies yielded inconsistent results with respect to success rate, onset time and duration of the block [8-17]. Several factors such as local anaesthetic volume/concentration ratio, anatomical site of injection and the nerve locating technique used in the study might have contributed to the variable results.

For the Labat approach to the sciatic nerve block using a single injection nerve stimulation technique, Taboada et al observed that 20 mL of mepivacaine 1.5% (vs 30 mL of mepivacaine 1%) improved the success rate and shortened the onset time of both sensory and motor block [9]. The authors speculated that, because of the size of sciatic nerve and the thickness of epineurium it would require a large concentration gradient to facilitate the diffusion of local anaesthetic molecules. In contrast, Cappelleri et al, using a double injection nerve stimulator technique for sciatic nerve block, found no difference with respect to success rate, onset time and duration of the block between 12 mL of mepivacaine 2% and 24 mL of mepivacaine 1% [15]. They hypothesized that compared to a single injection technique, the double injection resulted in better distribution of local anaesthetic around each component of the peripheral nerve and with this, the effect of local anaesthetic volume/concentration ratio become secondary to the regional nerve localisation technique.

Similarly, few studies have evaluated the effect of altering the volume and concentration of a fixed local anaesthetic dose for the brachial plexus block. Krenn et al suggested that higher volume of ropivacaine resulted in faster onset of motor block for a single injection axillary block, where loose connective tissue surrounds the brachial plexus [11]. In contrast, studies where the axillary block was performed using the multiple injection nerve stimulator technique [13] and infraclavicular block using ultrasound [14], did not show any difference with respect to block success rate and onset time. In our study, overall onset of surgical anaesthesia was faster using a higher volume when compared to a lower volume (identical dose), and this was mainly reflective of the onset of sensory but not motor component of the block. The difference in the result could be explained by the technique used to locate the target nerves. We performed the ultrasound guided axillary brachial plexus block having identified all four terminal nerves with the precise endpoint consisting of circumferential perineural spread of local anaesthetic, and not using a single or multiple nerve stimulation, or ultrasound guided perivascular approach [3,18].

Interestingly, and perhaps counterintuitively, the injection of the lower volume resulted in a longer block performance time. This is likely due to the requirement for a more precise needle tip positioning and subsequent adjustment in order to achieve circumferential spread around each of the four terminal nerves while having a limited injectate volume at disposal.

Our study is limited inter alia by the small sample size. Although we found differences between groups in terms of both onset time and duration of block, these results cannot be generalised to other local anaesthetics, techniques and peripheral injection sites due to variation in the anatomical architecture surrounding nerves [19-21]. It has been demonstrated that, using a multiple injection technique for a humeral canal block, higher volume and lower concentration of levobupivacaine improved the sensory block quality and success rate [16]. In contrast, ultrasound guided interscalene block resulted in faster onset of block using lower volume and higher concentration of ropivacaine [17].

In **conclusion**, when compared to 20 mL of lidocaine 2% with epinephrine, 40 mL of lidocaine 1% with epinephrine resulted in faster overall onset and shorter duration of surgical anaesthesia following an ultrasound guided axillary brachial plexus block. Further studies are required to determine whether these results can be extrapolated to other local anaesthetics and anatomical injection sites.

Acknowledgement: Assistance with this manuscript: Mr Bahman Honsari provided statistical expertise.

Conflicts of interest: none.

References

1. Sites BD, Beach ML, Spence BC, et al. Ultrasound guidance improves the success rate of a perivascular axillary plexus block. Acta Anaesthesiol Scand 2006;50:678-684.
2. Chan VW, Perlas A, McCartney CJ, et al. Ultrasound guidance improves success rate of axillary brachial plexus block. Can J Anaesth 2007;54:176-182.
3. Casati A, Danelli G, Baciarello M, et al. A prospective, randomized comparison between ultrasound and nerve stimulation guidance for multiple injection axillary brachial plexus block. Anesthesiology 2007;106:992-996.
4. O'Donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. Anesthesiology 2009;111:25-29.
5. Vester-Andersen T, Eriksen C, Christiansen C. Perivascular axillary block III: blockade following 40 ml of 0.5%, 1% or 1.5% mepivacaine with adrenaline. Acta Anaesthesiol Scand 1984;28:95-98.
6. Serradell A, Herrero R, Villanueva JA, et al. Comparison of three different volumes of mepivacaine in axillary plexus block using multiple nerve stimulation. Br J Anaesth 2003;91:519-524.
7. Casati A, Fanelli G, Aldegheri G, et al. Interscalene brachial plexus anaesthesia with 0.5%, 0.75% or 1% ropivacaine: a double-blind comparison with 2% mepivacaine. Br J Anaesth 1999;83:872-875.
8. Smith BE, Siggins D. Low volume, high concentration block of the sciatic nerve. Anaesthesia 1988;43:8-11.
9. Taboada Muñiz M, Rodríguez J, Bermúdez M, et al. Low volume and high concentration of local anesthetic is more efficacious than high volume and low concentration in Labat's sciatic nerve block: a prospective, randomized comparison. Anesth Analg 2008;107:2085-2088.
10. Vester-Andersen T, Christiansen C, Sørensen M, et al. Perivascular axillary block II: influence of injected volume of local anaesthetic on neural blockade. Acta Anaesthesiol Scand 1983;27:95-98.
11. Krenn H, Deusch E, Balogh B, et al. Increasing the injection volume by dilution improves the onset of motor blockade, but not sensory blockade of ropivacaine for brachial plexus block. Eur J Anaesthesiol 2003;20:21-25.
12. Brenner D, Iohom G, Mahon P, Shorten G. Efficacy of axillary versus infraclavicular brachial plexus block in preventing tourniquet pain. Eur J Anaesthesiol 2019;36:48-54.
13. Bertini L, Palmisani S, Mancini S, et al. Does local anesthetic dilution influence the clinical effectiveness of multiple-injection axillary brachial plexus block?: a prospective, double-blind, randomized clinical trial in patients undergoing upper limb surgery. Reg Anesth Pain Med 2009;34:408-413.
14. González AP, Bernucci F, Techasuk W, et al. A randomized comparison between 3 combinations of volume and concentration of lidocaine for ultrasound-guided infraclavicular block. Reg Anesth Pain Med 2013;38:206-211.
15. Cappelleri G, Ambrosoli AL, Turconi S, et al. Effect of local anesthetic dilution on the onset time and duration of double-injection sciatic nerve block: a prospective, randomized, blinded evaluation. Anesth Analg 2014;119:489-493.
16. Nuñez Aguado D, López Alvarez S, Salamanca Montaña ME, et al. [Brachial plexus block with levobupivacaine at the humeral canal: comparison of a small volume at high concentration with a large volume at low concentration]. Rev Esp Anestesiol Reanim 2005;52:529-535.
17. Zhai W, Wang X, Rong Y, Li M, Wang H. Effects of a fixed low-dose ropivacaine with different volume and concentrations on interscalene brachial plexus block: a randomized controlled trial. BMC Anesthesiol 2016;16:80.
18. Bernucci F, Gonzalez AP, Finlayson RJ, Tran DQ. A prospective, randomized comparison between perivascular and perineural ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med 2012;37:473-477.
19. Thompson GE, Rorie DK. Functional anatomy of the brachial plexus sheaths. Anesthesiology 1983;59:117-122.
20. Areeruk P, Karmakar MK, Reina MA, Mok LYH, Sivakumar RK, Sala-Blanch X. High-definition ultrasound imaging defines the paraneural sheath and fascial compartments surrounding the cords of the brachial plexus at the costoclavicular space and lateral infraclavicular fossa. Reg Anesth Pain Med 2021, DOI:10.1136/rapm-2020-102304.
21. Cornish PB, Leaper CJ, Hahn JL. The "axillary tunnel": an anatomic reappraisal of the limits and dynamics of spread during brachial plexus blockade. Anesth Analg 2007;104:1288-1291.
22. Cornish PB, Leaper C. The sheath of the brachial plexus: fact or fiction? Anesthesiology 2006;105:563-565.

Appendix II. Original data.

1. Chapter 3 original data

Patient characteristics

Subject	Group	Age, y	Sex M/F	BMI, Kg/m^2	ASA	Duration of surgery, mins	Site of surgery
1	1	59	M	27	I	18	Wrist
2	1	32	F	22.6	I	79	Hand
3	1	37	M	24	I	65	Wrist
4	2	82	F	28.2	II	50	Wrist
5	2	80	F	28.2	II	45	Wrist
6	1	26	M	30.1	I	90	Wrist
7	2	25	M	24.7	I	45	Hand
8	2	22	F	28.1	I	75	Wrist
9	2	73	F	25.7	II	60	Wrist
10	1	61	M	22.7	III	45	Wrist
11	2	52	F	29.4	II	65	Wrist
12	1	31	M	26.7	1I	40	Wrist
13	2	41	F	26.3	II	60	Wrist
14	1	38	F	22.4	II	60	Wrist
15	1	31	M	22.9	I	45	Wrist
16	1	50	F	28.1	II	45	Wrist
17	2	59	F	27.7	II	60	Wrist
18	2	19	M	29.1	I	40	Hand
19	1	59	F	24.5	II	60	Wrist
20	2	24	M	24.1	I	60	Hand
21	2	62	F	22.4	II	55	Wrist
22	2	73	M	33.5	II	60	Wrist
23	2	30	M	24.7	I	45	Forearm
24	1	59	F	26.3	II	50	Wrist
25	2	59	F	30.1	II	60	Wrist
26	1	69	F	25.3	II	75	Wrist
27	2	45	M	24.2	I	50	Wrist
28	1	72	F	22.1	II	75	Wrist
29	1	56	M	32.4	II	35	Wrist
30	1	54	F	28.1	I	45	Hand

Group 1=10 mL; Group 2= 30 mL

y = years; M=male; F=female; BMI= body mass index; ASA=American Society of Anaesthesiologist physical status grading

Sensory and motor block onset times of individual nerves in mins

Subject	Group	RN S	RN M	UN S	UN M	MN S	MN M	MCN S	MCN M	Overall Sensory	Overall Motor
1	1	10	20	10	10	10	10	10	5	10	20
2	1	15	10	10	10	15	10	5	5	15	10
3	1	15	10	15	15	15	10	5	5	15	10
4	2	15	5	5	5	15	5	15	15	15	15
5	2	5	5	5	5	5	5	5	5	5	5
6	1	30	25	10	10	5	25	30	10	30	25
7	2	5	5	5	5	10	5	5	5	10	5
8	2	10	15	5	10	10	5	5	5	10	15
9	2	15	5	5	5	5	5	5	5	15	5
10	1	20	15	15	10	15	5	10	10	20	15
11	2	10	5	5	5	10	5	10	5	10	5
12	1	15	10	15	10	15	10	15	5	15	10
13	2	15	5	15	5	5	5	5	5	15	5
14	1	15	5	15	15	10	10	15	15	15	15
15	1	5	5	5	10	5	10	5	5	5	10
16	1	10	5	5	5	5	5	5	5	10	5
17	2	5	5	5	5	5	5	5	5	5	5
18	2	5	5	5	10	5	5	5	10	5	10
19	1	5	5	5	5	5	5	5	10	5	10
20	2	5	5	5	5	5	5	5	5	5	5
21	2	5	5	5	5	5	5	5	5	5	5
22	2	15	15	15	15	10	10	10	10	15	15
23	2	5	5	5	5	10	10	5	5	10	10
24	1	15	15	10	10	15	15	10	10	15	15
25	2	5	5	5	5	5	5	5	5	5	5
26	1	15	10	5	10	10	10	10	5	15	10
27	2	10	10	10	10	5	5	5	5	10	10
28	1	10	5	10	5	10	5	10	5	10	5
29	1	10	10	10	15	15	15	10	10	15	15
30	1	15	15	10	15	15	15	10	10	15	15

Group 1=10 mL; Group 2= 30 mL; RN= radial nerve; UN=ulnar nerve; MN=median nerve; MCN=musculocutaneous nerve; S=sensory; M=motor

Sensory and motor block duration of individual nerves in mins

Subject	Group	RN S	RN M	UN S	UN M	MN S	MN M	MCN S	MCN M	Overall Sensory	Overall Motor
1	1	193	238	223	238	178	238	238	238	178	238
2	1	187	187	202	202	187	187	202	202	187	187
3	1	140	140	155	155	140	140	155	155	140	140
4	2	205	205	205	205	205	205	235	235	205	205
5	2	170	204	179	194	179	179	164	164	164	164
6	1	151	166	151	166	151	166	166	166	151	166
7	2	280	280	295	280	265	265	265	250	265	250
8	2	180	225	201	225	180	210	225	225	180	210
9	2	250	265	235	250	265	265	250	250	235	250
10	1	152	152	137	152	137	152	137	152	137	152
11	2	230	245	245	260	245	260	230	245	245	245
12	1	185	185	185	185	170	185	185	185	170	185
13	2	170	185	170	170	185	185	185	170	170	170
14	1	165	180	165	180	180	195	165	180	165	180
15	1	202	202	172	172	172	202	202	172	172	172
16	1	128	128	143	143	143	143	143	143	128	128
17	2	205	220	220	235	220	235	205	235	205	220
18	2	218	218	188	188	188	188	188	188	188	188
19	1	154	154	154	154	169	169	169	169	154	154
20	2	167	182	182	197	167	182	182	182	167	182
21	2	175	175	175	190	175	175	190	190	175	175
22	2	173	188	188	188	173	188	188	188	173	188
23	2	195	195	195	210	195	195	195	210	195	195
24	1	165	180	180	180	180	165	165	180	165	165
25	2	199	199	214	214	214	214	214	214	199	199
26	1	147	147	162	147	147	147	147	162	147	147
27	2	175	175	175	175	190	175	175	175	175	175
28	1	142	142	142	142	142	142	142	157	142	142
29	1	172	172	187	187	187	187	172	187	172	172
30	1	165	180	165	165	165	180	165	165	165	165

Group 1=10 mL; Group 2= 30 mL; RN= radial nerve; UN=ulnar nerve; MN=median nerve; MCN=musculocutaneous nerve; S=sensory; M=motor

Time to first request of postoperative analgesia in mins (TTFRA)

Subject	Group	TTFRA
1	1	256
2	1	192
3	1	165
4	2	Nil
5	2	384
6	1	170
7	2	Nil
8	2	290
9	2	Nil
10	1	160
11	2	300
12	1	Nil
13	2	200
14	1	190
15	1	Nil
16	1	263
17	2	Nil
18	2	Nil
19	1	186
20	2	222
21	2	325
22	2	243
23	2	Nil
24	1	Nil
25	2	225
26	1	190
27	2	Nil
28	1	157
29	1	330
30	1	180

Group 1=10 mL; Group 2= 30 mL

2. Chapter 4 original data

Patient characteristics

Subject	Group	Age, y	Sex, M/F	BMI, Kg/m^2	ASA	Duration of surgery, mins	Site of surgery
1	2	62	M	22.1	II	50	Wrist
2	1	79	F	24.6	II	60	Wrist
3	1	36	M	25.4	I	55	Wrist
4	2	26	M	27.4	I	45	Hand
5	2	66	M	33.1	II	60	Wrist
6	1	35	M	28.4	I	50	Hand
7	2	47	M	22.8	II	55	Hand
8	1	45	M	28.4	I	60	Hand
9	2	58	F	24.4	II	70	Wrist
10	1	24	M	24.8	I	75	Wrist
11	2	55	M	20.9	II	90	Wrist
12	1	54	M	27.3	I	80	Hand
13	1	35	M	29.3	II	60	Hand
14	2	21	M	23.1	I	45	Wrist
15	2	37	F	22.6	I	65	Wrist
16	2	63	M	27.3	II	65	Hand
17	1	61	F	22.2	II	70	Wrist
18	1	30	M	24.8	I	65	Hand
19	2	45	M	22.1	I	40	Hand
20	1	69	F	18.4	I	45	Wrist

Group 1=2%; Group 2= 1%

y = years; M=male; F=female; BMI= body mass index; ASA=American Society of Anaesthesiologist physical status grading

Sensory and motor block onset times of individual nerves in mins

Subject	Group	RN S	RN M	UN S	UN M	MN S	MN M	MCN S	MCN M	Overall Sensory onset	Overall Motor onset	Overall onset of block
1	2	5	7.5	5	7.5	5	7.5	2.5	5	5	7.5	7.5
2	1	5	2.5	5	2.5	5	2.5	5	2.5	5	2.5	5
3	1	5	5	5	2.5	5	2.5	5	2.5	5	5	5
4	2	7.5	5	7.5	7.5	5	7.5	5	5	7.5	7.5	7.5
5	2	2.5	7.5	2.5	7.5	5	7.5	5	7.5	5	7.5	7.5
6	1	10	7.5	7.5	7.5	7.5	5	10	10	10	10	10
7	2	5	5	5	5	2.5	5	5	5	5	5	5
8	1	10	7.5	7.5	5	7.5	5	5	5	10	7.5	10
9	2	2.5	2.5	2.5	2.5	2.5	5	2.5	2.5	2.5	5	5
10	1	5	5	7.5	5	5	7.5	5	5	5	7.5	7.5
11	2	7.5	2.5	7.5	2.5	7.5	2.5	7.5	2.5	7.5	2.5	7.5
12	1	20	22.5	15	12.5	15	12.5	15	12.5	20	22.5	22.5
13	1	2.5	2.5	2.5	5	10	5	2.5	5	10	5	10
14	2	2.5	2.5	2.5	7.5	5	7.5	5	7.5	7.5	7.5	7.5
15	2	2.5	2.5	5	2.5	2.5	2.5	2.5	2.5	5	2.5	5
16	2	2.5	2.5	5	2.5	2.5	2.5	2.5	2.5	5	2.5	5
17	1	10	2.5	5	2.5	10	2.5	10	2.5	10	2.5	10
18	1	5	5	5	2.5	5	7.5	5	2.5	5	7.5	7.5
19	2	5	5	5	5	5	5	2.5	5	5	5	5
20	1	5	2.5	7.5	5	2.5	2.5	2.5	2.5	2.5	5	7.5

Group 1=2%; Group 2= 1%; RN= radial nerve; UN=ulnar nerve; MN=median nerve; MCN=musculocutaneous nerve; S=sensory; M=motor

Sensory and motor block duration of individual nerves in mins

Subject	Group	RN S	RN M	UN S	UN M	MN S	MN M	MCN S	MCN M	Overall Sensory	Overall Motor	Overall duration of block
1	2	153	138	153	138	138	138	153	138	138	138	138
2	1	180	165	180	165	180	165	180	165	180	165	165
3	1	175	175	175	175	175	175	175	175	175	175	175
4	2	186	171	201	171	186	171	186	171	186	171	171
5	2	211	196	211	196	196	181	196	196	196	181	181
6	1	171	162	177	177	177	162	177	162	177	162	162
7	2	163	163	163	163	163	148	148	148	148	148	148
8	1	183	183	168	168	168	183	183	168	168	168	168
9	2	142	142	142	127	142	142	142	127	142	127	127
10	1	175	175	175	160	175	160	160	160	160	160	160
11	2	184	169	184	169	184	169	184	169	184	169	169
12	1	172	172	172	172	172	172	172	172	172	172	172
13	1	179	169	179	179	179	164	179	179	179	164	164
14	2	165	165	165	165	165	150	150	150	150	150	150
15	2	160	160	160	160	145	145	160	145	145	145	145
16	2	155	140	155	155	155	140	140	140	140	140	140
17	1	174	174	174	174	174	169	174	169	174	169	169
18	1	171	171	171	156	171	171	171	156	171	156	156
19	2	155	140	155	140	155	140	155	140	155	140	140
20	1	175	160	175	160	160	160	160	160	160	160	160

Group 1=2%; Group 2= 1%; RN= radial nerve; UN=ulnar nerve; MN=median nerve; MCN=musculocutaneous nerve; S=sensory; M=motor

Block performance data

Subject	Group	Imaging time, mins (A)	Needling time, mins (B)	Performance time, mins (A+B)	Needle passes, n	Vascular puncture, n	Parasthesia, n
1	2	3	6	9	8	0	0
2	1	2.5	9.5	12	12	0	0
3	1	2.58	9.5	12.08	13	0	0
4	2	2.45	6.75	9.2	7	0	1
5	2	1.66	6.84	8.5	7	0	0
6	1	1.66	8.42	10.08	13	1	1
7	2	3	5	8	8	0	0
8	1	2	7	9	8	0	0
9	2	2.5	6.5	9	8	0	1
10	1	2.25	10.75	13	14	0	2
11	2	2	7.8	9.8	8	0	0
12	1	2.5	7.5	10	9	1	1
13	1	2	8	10	8	0	0
14	2	1.03	8.27	9.3	7	1	0
15	2	2.5	7	9.5	6	0	0
16	2	3	6	9	5	0	0
17	1	3	7	10	9	0	0
18	1	3	9	12	8	0	0
19	2	2.5	7	9.5	8	0	0
20	1	3.16	8	11.6	11	0	1

Group 1=2%; Group 2= 1%

3. Chapter 5 original data set

Patient characteristics

Subject	Group	Age, y	Sex M/F	BMI, Kg/m^2	ASA	Duration of surgery, mins	Site of surgery
1	2	41	F	24.4	II	74	Wrist
2	2	38	M	25.3	I	21	Hand
3	1	61	M	25.4	I	93	Wrist
4	1	43	M	25.2	I	69	Wrist
5	2	28	M	24	I	83	Hand
6	2	36	F	25.7	I	68	Wrist
7	1	48	F	29.4	I	80	Hand
8	2	54	F	30.1	II	60	Wrist
9	2	41	M	25.9	I	70	Hand
10	1	42	M	28.1	I	75	Wrist
11	1	22	M	25.1	I	65	Wrist
12	1	45	F	25.6	I	65	Wrist
13	2	49	M	25.8	II	60	Hand
14	1	52	F	22.7	II	75	Hand
15	1	41	F	23.3	I	45	Wrist
16	2	42	M	25.8	I	65	Wrist
17	1	29	F	25.6	I	45	Wrist
18	1	47	M	26	II	65	Wrist
19	2	51	F	21.7	II	50	Wrist
20	2	55	M	26.6	II	60	Hand
21	1	32	M	26.3	I	45	Wrist
22	1	35	M	26.9	II	45	Wrist
23	2	42	M	26.2	I	70	Forearm
24	2	31	M	27.8	I	60	Wrist

Group 1 = 20 mL of lidocaine 2% plus 1:200,000 epinephrine and 2 mL of 0.9% normal saline.

Group 2= 20 mL of lidocaine 2% plus 1:200,000 epinephrine and 2 mL of clonidine 1 µg/kg in 0.9% normal saline

y = years; M=male; F=female; BMI= body mass index; ASA=American Society of Anaesthesiologist physical status grading

Sensory and motor block onset times of individual nerves in mins

Subject	Group	RN S	RN M	UN S	UN M	MN S	MN M	MCN S	MCN M	Overall Sensory	Overall Motor	Overall onset of block
1	2	5	5	5	5	5	5	5	5	5	5	5
2	2	2.5	2.5	2.5	2.5	2.5	2.5	5	5	5	5	5
3	1	7.5	5	10	7.5	10	7.5	7.5	5	10	7.5	10
4	1	10	7.5	10	7.5	7.5	7.5	7.5	7.5	10	7.5	10
5	2	7.5	5	5	5	7.5	5	7.5	5	7.5	5	7.5
6	2	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	1	15	5	2.5	2.5	12.5	7.5	10	2.5	15	7.5	15
8	2	7.5	5	7.5	5	7.5	5	7.5	5	7.5	5	7.5
9	2	7.5	5	7.5	5	7.5	5	7.5	2.5	7.5	5	7.5
10	1	10	7.5	10	7.5	12.5	7.5	10	7.5	12.5	7.5	12.5
11	1	7.5	5	7.5	5	10	12.5	7.5	2.5	10	12.5	12.5
12	1	12.5	5	10	5	12.5	5	7.5	5	12.5	5	12.5
13	2	5	2.5	7.5	2.5	5	2.5	5	2.5	7.5	2.5	7.5
14	1	5	5	5	5	7.5	5	7.5	5	7.5	5	7.5
15	1	5	2.5	7.5	5	7.5	2.5	7.5	2.5	7.5	5	7.5
16	2	2.5	2.5	5	2.5	5	5	2.5	2.5	5	5	5
17	1	10	7.5	7.5	5	7.5	5	5	5	10	7.5	10
18	1	10	7.5	10	7.5	7.5	5	5	5	10	7.5	10
19	2	5	5	5	5	5	2.5	2.5	5	5	5	5
20	2	7.5	7.5	5	5	7.5	5	5	7.5	7.5	7.5	7.5
21	1	12.5	5	7.5	5	5	5	10	7.5	12.5	7.5	12.5
22	1	7.5	7.5	7.5	5	7.5	5	7.5	2.5	7.5	7.5	7.5
23	2	5	2.5	5	2.5	5	2.5	5	2.5	5	2.5	5
24	2	5	2.5	5	2.5	5	2.5	5	2.5	5	2.5	5

RN= radial nerve; UN=ulnar nerve; MN=median nerve; MCN=musculocutaneous nerve; S=sensory; M=motor

Sensory and motor block duration of individual nerves in mins

Subject	Group	RN S	RN M	UN S	UN M	MN S	MN M	MCN S	MCN M	Overall Sensory	Overall Motor	Overall duration of block
1	2	249	249	249	249	249	249	264	264	249	249	249
2	2	201	186	201	186	201	201	216	201	201	186	186
3	1	188	188	188	188	188	188	203	203	188	188	188
4	1	165	180	180	180	165	165	165	165	165	165	165
5	2	273	273	273	273	273	273	273	273	273	273	273
6	2	228	228	228	228	228	228	228	228	228	228	228
7	1	195	180	210	195	195	210	195	195	195	180	180
8	2	180	180	180	180	180	180	180	180	180	180	180
9	2	233	233	233	233	233	233	233	233	233	233	233
10	1	195	195	195	195	195	195	195	195	195	195	195
11	1	136	151	136	136	151	151	151	151	136	136	136
12	1	150	150	150	150	150	150	150	150	150	150	150
13	2	178	223	178	223	178	223	178	223	178	223	178
14	1	133	133	118	133	118	118	118	118	118	118	118
15	1	206	191	206	191	191	191	206	191	191	191	191
16	2	198	198	198	198	198	213	213	213	198	198	198
17	1	184	184	184	184	184	199	184	199	184	184	184
18	1	186	186	186	171	186	186	186	171	171	171	171
19	2	225	225	240	225	225	225	240	225	225	225	225
20	2	225	225	225	225	240	225	240	225	225	225	225
21	1	146	146	161	146	161	161	161	161	146	146	146
22	1	160	160	175	175	175	160	175	160	160	160	160
23	2	227	227	242	227	242	242	242	227	227	227	227
24	2	217	217	217	232	232	217	232	217	217	217	217

RN= radial nerve; UN=ulnar nerve; MN=median nerve; MCN=musculocutaneous nerve; S=sensory; M=motor

Time to first request of postoperative analgesia in mins (TTFRA)

Subject	Group	TTFRA
1	2	290
2	2	Nil
3	1	Nil
4	1	200
5	2	315
6	2	618
7	1	510
8	2	Nil
9	2	Nil
10	1	295
11	1	154
12	1	210
13	2	Nil
14	1	143
15	1	Nil
16	2	Nil
17	1	241
18	1	208
19	2	Nil
20	2	320
21	1	Nil
22	1	Nil
23	2	Nil
24	2	Nil

Systolic blood pressure changes (mmHg)

Subject	Group	Baseline	5	10	15	20	25	30	35	40	45	50	55	60	90	120	150	180	210	240
1	2	121	136	131	121	124	118	131	121	125	125	126	125	121	136	121	118	121	133	125
2	2	118	125	129	118	126	131	132	129	120	121	120	121	118	125	118	120	118	136	120
3	1	122	124	130	126	128	137	120	127	134	128	118	128	118	113	125	128	127	120	134
4	1	133	121	135	112	131	133	132	132	129	124	130	124	128	137	120	118	134	128	129
5	2	134	121	122	134	135	133	136	134	118	118	133	118	134	121	134	129	134	125	118
6	2	138	118	133	138	133	136	136	129	134	134	136	134	138	118	138	127	138	121	134
7	1	141	134	138	136	132	133	124	130	126	128	137	128	118	134	128	118	131	136	126
8	2	142	127	136	142	136	125	125	133	138	138	125	138	142	134	142	120	142	118	138
9	2	143	124	125	143	135	133	121	125	142	142	121	142	143	138	143	132	143	136	142
10	1	124	122	126	131	131	131	136	132	133	131	127	131	126	131	125	133	133	125	133
11	1	136	124	130	126	128	132	120	121	134	128	118	128	131	129	131	136	138	121	134
12	1	137	122	127	137	133	129	136	137	132	133	143	133	137	117	137	125	137	118	132
13	2	129	133	121	129	121	138	118	129	131	143	118	143	129	142	129	124	129	125	131
14	1	125	120	128	125	122	125	125	125	126	137	136	137	125	119	125	121	125	134	126
15	1	118	132	120	118	134	121	121	118	127	125	132	125	118	120	118	118	118	138	127
16	2	131	136	118	131	128	134	134	131	134	129	121	129	131	124	131	128	131	121	134
17	1	122	124	132	122	128	118	118	122	126	118	127	118	122	132	122	121	122	142	126
18	1	133	131	124	133	120	134	134	133	120	122	120	122	133	124	133	120	133	129	120
19	2	132	125	131	132	133	138	138	136	138	131	127	131	132	120	132	120	132	118	138
20	2	136	121	129	136	129	137	142	136	142	132	132	132	136	133	136	131	136	134	142
21	1	136	120	127	136	127	138	138	136	132	133	132	133	136	135	136	132	136	120	132
22	1	125	133	120	125	124	131	142	125	124	136	124	136	125	120	125	124	125	118	124
23	2	127	118	132	128	129	129	118	129	118	143	121	143	118	129	118	143	141	145	118
24	2	129	135	140	125	126	129	131	133	134	132	126	132	128	129	126	127	122	133	134

Diastolic blood pressure changes (mmHg)

Subject	Group	Baseline	5	10	15	20	25	30	35	40	45	50	55	60	90	120	150	180	210	240
1	2	81	79	66	72	81	72	67	58	74	64	69	81	73	58	58	64	58	64	64
2	2	64	81	69	71	74	64	69	73	75	74	74	64	69	73	73	74	73	64	74
3	1	77	66	76	72	72	72	77	77	77	77	73	77	77	77	77	72	77	72	72
4	1	64	64	69	77	77	77	64	64	64	64	74	64	64	64	64	77	64	77	77
5	2	64	77	69	69	71	75	77	74	73	72	74	64	69	74	74	74	74	74	74
6	2	74	71	73	72	69	71	58	69	74	64	62	74	64	69	76	76	69	74	76
7	1	64	67	68	64	64	64	77	77	58	72	69	64	77	77	77	64	77	64	64
8	2	77	69	76	74	72	71	71	73	69	77	64	77	69	73	73	74	73	76	74
9	2	77	66	77	76	74	71	58	78	73	64	69	77	69	78	78	72	78	74	73
10	1	72	71	66	77	77	77	77	72	72	72	73	72	72	72	72	77	72	77	77
11	1	77	73	67	64	72	64	64	77	77	77	78	77	77	77	77	64	77	64	64
12	1	64	74	69	64	77	64	77	64	64	64	79	64	64	64	64	64	64	64	64
13	2	69	69	71	77	76	75	77	79	78	74	64	69	81	79	79	77	79	72	74
14	1	77	58	72	77	64	77	72	77	77	77	69	77	77	77	77	74	77	74	74
15	1	64	73	73	77	77	77	77	64	64	64	64	64	64	64	64	72	64	74	74
16	2	74	73	72	75	77	75	77	69	79	76	74	74	64	69	81	64	69	77	69
17	1	64	74	74	81	64	64	64	64	64	64	64	64	64	64	64	77	64	76	76
18	1	74	76	75	78	64	64	77	69	74	64	69	74	64	69	77	64	69	74	74
19	2	64	75	74	74	64	69	74	77	69	77	74	64	69	77	77	77	77	64	73
20	2	64	76	77	71	58	72	77	64	58	72	77	64	74	64	69	64	64	77	78
21	1	78	73	72	77	77	77	64	73	74	77	69	78	74	73	75	77	73	64	77
22	1	79	78	69	81	77	73	64	74	76	64	68	79	58	74	74	64	74	77	64
23	2	72	77	69	71	58	72	77	64	68	71	58	72	77	64	69	64	64	64	79
24	2	77	72	71	71	58	72	77	71	71	58	72	77	64	71	58	74	71	64	69

Heart rate changes

Subject	Group	Baseline	5	10	15	20	25	30	35	40	45	50	55	60	90	120	150	180	210	240
1	2	77	76	75	75	70	73	75	76	74	70	73	75	76	77	75	77	75	75	74
2	2	76	75	75	75	70	73	75	73	75	76	70	73	75	76	74	75	76	74	73
3	1	75	77	77	74	76	75	74	76	77	78	77	78	77	75	75	73	72	69	70
4	1	74	75	74	77	77	78	77	78	77	75	77	75	75	74	76	77	78	77	78
5	2	72	69	70	69	68	66	69	72	71	69	70	66	69	72	71	69	70	66	69
6	2	73	72	69	72	70	71	72	73	71	69	70	70	72	73	76	77	78	77	78
7	1	75	76	76	78	78	77	78	76	77	78	77	78	76	75	70	73	75	76	73
8	2	71	72	69	73	70	72	73	75	76	77	73	71	72	71	73	77	78	77	78
9	2	71	72	76	72	66	69	72	71	69	70	66	69	72	71	69	70	66	69	69
10	1	73	70	72	72	66	69	72	71	69	70	66	69	70	73	75	76	73	72	71
11	1	76	75	75	73	75	76	73	75	73	75	70	73	75	76	75	76	72	71	70
12	1	77	75	76	76	73	75	76	70	73	75	76	74	75	77	74	70	73	75	76
13	2	71	72	69	72	66	69	72	71	69	65	66	69	72	71	69	70	66	69	71
14	1	75	67	71	71	66	70	71	69	69	70	71	72	67	75	78	77	72	73	75
15	1	73	70	69	72	66	69	72	71	69	70	66	69	70	73	75	76	70	69	71
16	2	65	69	70	69	65	66	69	72	71	69	70	66	69	65	66	69	72	71	69
17	1	77	78	77	77	77	75	77	75	75	74	78	77	78	77	75	77	75	75	74
18	1	72	71	69	70	71	73	70	69	69	71	69	68	71	72	73	74	73	71	70
19	2	76	74	78	77	74	76	77	78	77	78	74	79	74	76	77	78	77	78	69
20	2	77	79	76	74	78	77	74	76	77	78	77	78	79	77	76	75	73	74	77
21	1	77	74	76	78	78	77	78	77	75	77	75	75	74	77	75	77	75	75	74
22	1	70	75	75	75	70	73	75	76	74	77	78	73	75	70	73	75	76	72	71
23	2	76	74	76	78	76	77	78	77	78	81	82	78	74	76	77	78	77	78	78
24	2	78	77	71	78	78	77	78	70	73	75	76	76	77	78	79	74	75	77	74

SpO2 changes

Subject	Group	Baseline	5	10	15	20	25	30	35	40	45	50	55	60	90	120	150	180	210	240
1	2	97	96	96	96	94	95	95	95	95	96	97	96	97	97	96	95	97	96	96
2	2	96	97	97	96	96	94	95	95	95	96	96	97	96	97	97	95	97	96	96
3	1	96	97	96	95	96	97	97	95	95	96	95	96	96	97	97	95	97	96	97
4	1	97	96	97	97	96	96	97	96	96	97	96	96	97	96	97	96	97	97	98
5	2	96	97	95	94	93	94	95	94	94	95	95	96	96	97	96	94	97	95	96
6	2	96	97	96	96	96	97	96	97	97	97	96	97	96	97	97	97	96	97	97
7	1	97	97	96	96	97	96	97	97	97	96	97	96	97	97	97	97	97	96	96
8	2	97	96	97	97	96	97	97	97	97	97	97	96	97	97	97	97	97	97	97
9	2	97	95	94	95	97	95	96	96	96	97	96	97	97	97	96	96	97	97	97
10	1	96	96	95	94	93	95	95	94	94	95	96	97	96	97	95	94	96	95	97
11	1	96	97	97	97	96	96	97	96	96	97	97	97	96	97	97	96	97	97	96
12	1	97	96	97	97	96	97	96	96	96	97	96	97	97	97	97	97	96	97	96
13	2	97	97	96	97	97	96	97	96	96	97	96	96	97	96	97	96	96	97	96
14	1	97	96	95	95	94	95	95	96	96	96	96	96	97	97	97	96	97	96	97
15	1	97	97	95	95	94	95	95	96	96	96	96	96	97	97	97	96	97	96	96
16	2	96	96	97	97	95	96	96	96	96	96	97	97	96	96	96	96	97	96	98
17	1	97	96	97	96	97	97	96	97	97	97	97	96	97	96	97	97	96	97	96
18	1	96	97	96	95	95	94	95	95	95	97	96	96	96	97	97	95	97	97	96
19	2	97	97	96	97	97	96	97	97	97	97	97	96	97	96	97	97	97	97	96
20	2	96	97	96	97	97	96	96	97	97	97	97	97	96	97	96	97	97	97	96
21	1	96	96	96	96	96	97	96	97	97	97	96	97	96	97	97	97	97	97	96
22	1	97	96	96	95	96	96	94	95	95	95	96	96	97	96	97	95	96	95	96
23	2	97	96	96	96	97	96	97	97	97	96	97	96	97	97	97	97	97	96	96
24	2	96	96	94	95	95	95	96	96	96	96	97	97	96	97	97	96	97	96	97

Sedation score

Subject	Group	Baseline	5	10	15	20	25	30	35	40	45	50	55	60	90	120	150	180	210	240
1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	2	0	0	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
6	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	2	0	0	0	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
10	1	0	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0
11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	1	0	0	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0	0
15	1	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
16	2	0	0	0	1	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0
17	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	1	0	0	0	1	1	0	1	0	1	1	1	1	1	0	0	0	0	0	0
19	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0