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υπό

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Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

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Ευχαριστίες

Θα ήθελα να ευχαριστήσω θερμά τον διευθυντή μου, και διευθυντή αυτού του μεταπτυχιακού τίτλου σπουδών καθ.Αθ.Γιαννούκα, για όλες τις ευκαιρίες που μου έχει προσφέρει, μαζί σε αυτές και η συμμετοχή μου σε αυτό τον μεταπτυχιακό τίτλο σπουδών. Θερμότερα θα ήθελα να ευχαριστήσω το δάσκαλο μου και επιβλέποντα αυτής της μεταπτυχιακής εργασίας Αν. Καθ. Γ. Κούβελο, για την καθοδήγηση του και το χρόνο που αφιέρωσε για να έρθει εις πέρας αυτή η διπλωματική εργασία.

Περίληψη

Η δημιουργία μιας αρτηριοφλεβικής επικοινωνίας στα άνω άκρα είναι συχνά η επέμβαση πρώτης επιλογής σε ασθενείς που χρήζουν αιμοκάθαρσης. Οι επικοινωνίες αυτές έχουν υψηλά ποσοστά αποτυχίας ωρίμανσης, τα οποία εξαρτώνται από την αιματική παροχή της δότριας αρτηρίας. Σε ασθενείς που χειρουργούνται υπό γενική ή υπό τοπική αναισθησία, η αυξημένη συμπαθητική δραστηριότητα διεγχειρητικά αλλά και μετεγχειρητικά, οδηγεί σε σπασμό της αρτηρίας, με αποτέλεσμα αύξηση του ποσοστού αποτυχίας της επέμβασης. Με την επιλογή του υπερηχογραφικά καθοδηγούμενου νευρικού αποκλεισμού του βραχιονίου πλέγματος, και του συνεπακόλουθου αποκλεισμού των συμπαθητικών νευρικών ινών, αυξάνεται (λόγω αγγειοδιαστολής) η αιματική παροχή τόσο της δότριας αρτηρίας όσο και της απαγωγού φλέβας.

Στο πλαίσιο αυτό διενεργήθηκε μία συστηματική ανασκόπηση της βιβλιογραφίας και μετα-ανάλυση προοπτικών τυχαιοποιημένων μελετών σχετικά με τις επιπτώσεις του υπερηχογραφικά καθοδηγούμενου νευρικού αποκλεισμού του βραχιονίου πλέγματος στη δημιουργία αρτηριοφλεβικής επικοινωνίας σε αιμοκαθαιρόμενους ασθενείς. Η συστηματική ανασκόπηση έγινε στις βάσεις PubMed, Scopus and Cochrane Library και συμπεριελήφθησαν σε αυτή 9 μελέτες με συνολικό αριθμό 896 ασθενών, ενώ σε 5 από αυτές τις μελέτες πραγματοποιήθηκε και μετα-ανάλυση.

Το πρωτεύον καταληκτικό συμπέρασμα ήταν η βατότητα της αρτηριοφλεβικής επικοινωνίας στους 3 μήνες, ενώ δευτερεύοντα συμπεράσματα αποτελούσαν η άμεση μετεγχειρητική βατότητα και οι άμεσες μετεγχειρητικές επιπλοκές. Οι ασθενείς που χειρουργήθηκαν υπό υπερηχογραφικά καθοδηγούμενο νευρικό αποκλεισμό (ομάδα Α) φάνηκε ότι έχουν καλύτερα αποτελέσματα όσο αναφορά τη βατότητα στους 3 μήνες [Λόγος πιθανοτήτων (OR) 3.50, 95% διάστημα εμπιστοσύνης (CI): 1.96 έως 6.26, $p < 0.001$] σε σχέση με αυτούς που χειρουργήθηκαν υπό τοπική αναισθησία (ομάδα Β). Η ομάδα Α φάνηκε να υπερτερεί τόσο στην άμεση βατότητα (OR 4.96, 95% CI: 2.01 έως 12.25, $p < 0.001$), όσο και στις άμεσες επιπλοκές (OR 0.25, 95% CI: 0.07 έως 0.86, $p < 0.05$).

Συμπερασματικά ο υπερηχογραφικά καθοδηγούμενος αποκλεισμός του βραχιονίου πλέγματος φαίνεται να υπερτερεί έναντι της τοπικής αναισθησίας αναφορικά με τη μετεγχειρητική βατότητα και τον αριθμό των επιπλοκών.

Abstract

The creation of an arteriovenous fistula in the upper extremities is often the first-choice procedure for patients requiring hemodialysis. These fistulas have high rates of maturation failure, as a result of diminished blood supply from the donor artery. In patients undergoing surgery under general or local anesthesia, increased sympathetic activity intraoperatively and postoperatively may lead to arterial spasm, resulting in a higher failure rate of the procedure. By choosing ultrasound-guided brachial plexus nerve block and the consequent sympathetic nerve block, blood flow to both the donor artery and the outflow vein is increased (because of vasodilation).

A systematic review of the literature and a meta-analysis of prospective randomized studies were conducted to examine the effects of ultrasound-guided brachial plexus block on the creation of arteriovenous fistulas in hemodialysis patients. The systematic review included studies published in the PubMed, Scopus, and Cochrane Library databases, and incorporated nine studies with a total of 896 patients, while five of these studies were subsequently included in the meta-analysis.

The primary outcome was arteriovenous fistula patency at three months, while secondary outcomes included immediate postoperative patency and immediate postoperative complications. Patients who underwent surgery under ultrasound-guided nerve block (Group A) demonstrated better outcomes regarding patency at three months [Odds Ratio (OR) 3.50, 95% Confidence Interval (CI): 1.96 to 6.26, $p < 0.001$] compared to those who underwent surgery under local anaesthesia (Group B). Group A also showed superiority in terms of immediate patency (OR 4.96, 95% CI: 2.01 to 12.25, $p < 0.001$) and immediate complications (OR 0.25, 95% CI: 0.07 to 0.86, $p < 0.05$).

In conclusion, ultrasound-guided brachial plexus nerve block appears to be superior to local anesthesia in terms of postoperative patency and rate of complications.

Keywords: Arteriovenous fistula, Regional anaesthesia, Brachial plexus block, Meta-analysis, Systematic review

1.0 Introduction

A well-functioning hemodialysis access is crucial for patients with end stage chronic renal disease, and in most cases an arteriovenous fistula (AVF) is the modality of choice [1]. The most important factors in AVF are adequate function, durability and a low complication rate, and the best results can be achieved mainly by autologous fistulas of the upper extremities [2]. Up to one third of the fistulas are unsuccessful due to low quality (mostly in terms of diameter) of distal veins, and inadequate arterial blood flow, factors that are common in patients with end stage renal failure [3,4].

The likelihood of an AVF maturation is determined by a series of factors, most of which can be identified by pre-operative, intra and post-operative use of ultrasonography, such as diameter of both the vein and the artery, arterial inflow and the early postoperative flow through the immature fistula [5]. The choices regarding the type of anesthesia used to create an AVF may vary, and can include general, regional and local anesthesia, although the latter two are the most widely preferred by both surgeons and patients [6]. General anesthesia can have a positive influence in the process of an AVF creation through the induction of vasodilation, but in high-risk patients it is associated with increased risk for cardiovascular and respiratory complications [7]. To reduce the risks related with general anesthesia, both regional (brachial plexus block, BPB) and local anesthesia can be used as alternatives. Regional anaesthesia may have the desired sympathetic nerve block, which can lead, both intraoperatively and in the early postoperative period, to increased arterial blood flow as well as increased venous diameter [8]. Maintaining adequate inflow and outflow to the newly created fistula is a crucial factor in the maturation process, while at the same time may prevent early thrombosis and failure [9].

The use of ultrasound (U/S) plays a significant role, both in the pre-and intraoperative evaluation of the target vessels to better guide the surgeon's decision, as well as in the assessment of the neural bundle. Ultrasound guided brachial plexus block performs better regarding the success rate, safety (avoidance of vessel or pleura trauma) and total volume of drugs administered [10]. Several approaches are available to perform a brachial plexus block for AVF creation under U/S guidance: interscalene, axillar, supraclavicular and infraclavicular [10]. No consensus exists yet on the best approach, or the best combination of drugs administered during the procedure (which includes but are not limited at: Lidocaine, Papaverine, L-bupivacaine and Ropivacaine, in various concentrations and dosages) [11]. Although several studies have shown an

advantage of the regional over the local anesthesia in AVF creation, most of these studies include a small pool of patients and seem inadequate to lead to robust conclusions [11-15].

2.0 Arteriovenous fistula (AVF)

2.1 General Principles

The essential characteristics of a well-functioning arteriovenous fistula (AVF), needed to provide adequate blood flow and allow for easy cannulation during hemodialysis, are the following:

Blood flow: The flow in the AVF should be more than 600 ml/min. Well-functioning AVFs typically have a flow rate between 800 ml/min and 1200 ml/min.

Cannulation: The section used for cannulation of the AVF must consist of a straight vein segment, longer than 10 cm or in cases where that is not possible, two straight segments of at least 4 cm each, allowing for the placement of two large bore needles.

Diameter: The diameter of the cannulated section should be greater than 6 mm to facilitate easy and safe cannulation, during every session of hemodialysis.

Depth: The segment of the vein used for the creation of the AVF and the subsequent cannulation should be superficial, less than 6 mm from the skin surface, to ensure easy access [16].

2.2 The role of ultrasound examination during the preoperative evaluation – mapping

To construct an arteriovenous fistula with the best possible parameters (type, diameter of the artery and vein, depth, lack of vascular stenosis) and to ensure optimum result for the patient, preoperative examination of the vasculature of the upper arm is recommended before any type of surgery [17]. The operator, either the surgeon who will perform the operation, or a radiologist should be well-trained and have a thorough understanding of the vascular anatomy of the arm, including any potential important anatomical variations. They should be also knowledgeable about the various transducers, proper positioning, and the different modes of the ultrasound (namely B-mode and Doppler mode, which are the most frequently used), as well as hemodynamic physiology, to ensure accurate, bias-free results [18].

2.2.1 Patient position

Patients should be positioned comfortably, either seated (with the arm resting on a pillow for support) or lying down, with the examination area fully exposed. The upper extremity should be abducted, with the palm facing upwards. Patients should be in a relaxing state. The room temperature, as well as the transducer should be maintained at a warm level, as cold or excessive stress can lead to vascular constriction, altering the final measurements. Application of a tourniquet before the examination is recommended [19].

2.2.2 Transducer

For optimal vascular evaluation, a high-frequency linear Doppler ultrasound transducer is the preferred choice. In cases involving obese patients, patients with upper extremity edema or when assessing central vessels, a convex probe may be required [19].

2.2.3 Scanning techniques – Doppler settings

Ultrasound with the use of Doppler mode is a highly valuable preoperative tool for assessing the vasculature, as it enables the identification and optimal visualization of flow direction, volume flow and blood velocities, both in the venous and arterial system, therefore facilitating the detection of vascular stenosis, or cases of low flow, that would have prevented the fistula maturation. Transducer positioning is critical to reduce bias and artifacts, with the proper insonation angle ranging from 45 to 60 degrees, while also ensuring that the angle correction cursor aligns with the blood flow direction in a parallel manner. Errors in those simple but important parameters can introduce great inaccuracies in velocity measurements. Image quality can be further enhanced by proper steering and size of the color box. Another important step is confirming color configuration and determining flow direction (especially in complex cases), which may vary from the usual color coding: typically, red color indicates flow towards the transducer, while blue color indicates flow away from the transducer. Last but not least, the sample volume length should be correctly adjusted (ideally the sample size includes 50-70% of the vessel diameter), to calculate volume flow with better accuracy [19].

2.2.4. Evaluation of the venous system

Adequate knowledge of the complex venous anatomy of the upper arm is crucial in preoperative planning. Venous circulation of the upper arm is dichotomized in superficial and deep circulation, with the superficial veins being the major component for the arteriovenous fistula creation. The superficial venous system is comprised of the cephalic vein (lateral position) and the basilic vein (medial position). The cephalic vein (which is preferred for AVF creation due to more superficial position) drains the dorsal surface of the hand and extends laterally along the forearm before creating a junction with the axillary vein. On the other hand, the basilic vein drains the palmar surface of the hand and continues medially through the forearm, before joining the brachial vein, or depending on the anatomical variation, draining directly into the axillary vein [20].

Although both veins are considered superficial, the basilic vein penetrates the fascia at the proximal forearm, traveling in a deeper level, which makes correct puncture and needle insertion during hemodialysis difficult, or even impossible. When lacking other options, selection of the basilic vein for AVF creation often necessitates a second surgical procedure (either superficialization or transposition) and may lead to longer maturation periods. For these reasons cephalic vein is the target vessel of choice, but surgeons must always account for potential anatomic variations found on Doppler to ensure optimum results [20].

As far as the deep vein system is concerned, it is usually utilized only in complex access cases, when patients are lacking autologous vein material, either due to anatomical variations or previous access surgeries. The deep venous circulation consists of veins running alongside the radial and ulnar arteries, typically converging at the elbow to form the deep brachial veins. These veins pairing the brachial artery subsequently drain into the axillary and subclavian veins. In these scenarios, where the deep system is utilized, synthetic grafts are mostly required, such as axillary artery-to-axillary vein graft or brachial artery-to-brachial vein grafts [21].

Both the superficial and the deep vein system should be evaluated in every patient at the planning stage. This evaluation involves (but is not limited to) confirming vein patency, which is done by applying pressure to the veins, using the transducer, to examine if they are fully compressible, and with the simultaneous use of color doppler. Another very important predictive factor is the measurement of vein diameter, as studies have reported that it impacts significantly the prognosis and the durability of vascular access. While current guidelines do not specify a cut-off value for AVF

creation, a diameter greater than 2mm is associated with improved post-operative results in several studies [22,23]. With the application of a tourniquet the operator can identify better venous diameters, which also gives information about venous distensibility and serves as a positive prognostic factor when the distension capacity exceeds 40% [22,23].

A very important part of the preoperative ultrasound venous examination is exclusion of central venous stenosis or obstruction, which can become quite challenging particularly in cases of subclinical stenosis. The subclavian vein can be usually adequately visualized from the infraclavicular or the supraclavicular fossa, although lacking the ability to compress the vein in its entirety. This results in patency assessment using spectral Doppler, which during respiratory movements should be displaying spontaneous phasic flow if no outflow obstruction is present [23,24].

2.2.5 Evaluation of the arterial system

2.2.5.1 Anatomy of the arterial system of the upper extremities

The arterial circulation of the hands is mostly supplied by the subclavian artery, which continues to the axillary artery (between the clavicle and the first rib), and then progresses distally to the brachial artery. Brachial artery then typically bifurcates into the radial and ulnar artery 1-2 cm below the elbow, but as is often the case, this bifurcation occurs more proximally or distally. The radial artery traverses the forearm laterally, while the ulnar artery medially, having a confluence distally, ultimately forming the palmar arch [25].

2.2.5.2 Ultrasound evaluation of the arteries

As was the case with the venous circulation, ultrasound examination of the arteries, using mainly B-Mode and Doppler, should be performed pre-operatively in all patients. Arterial flow patterns, patency and diameter should be closely examined. The operator must be able to identify signs of arterial disease, such as calcification (usually seen as hyperechogenic vessels, with or without an acoustic shadow), stenosis (manifested as significant increase in peak systolic velocity, and irregular flow patterns (upper arm consists of high-resistance arteries producing a triphasic flow pattern in Doppler, therefore changes in that pattern, usually biphasic or monophasic flow, are strong indicators of peripheral arterial disease). Peak systolic velocity of the radial artery below 50cm/s and flow rate below 50ml/min have been associated with higher rates of primary fistula failure [25-27].

Not only Doppler parameters but also arterial diameter has been correlated with higher rates of fistula maturation. Although no consensus exists regarding a cut-off point, it is accepted that arterial diameter lower than 15mm increases the rate of fistula failure. This does not, though, in itself, preclude fistula creation and the operator should consider all the parameters before making a final decision. Another useful parameter is the existence of reactive hyperemia. This involves calculating the resistance index of the target artery and then having the patient clench their fist for 2 minutes. A decrease in the resistance index below 0.7 after this test is considered a good prognostic sign for fistula creation [25-27].

3.0 Brachial Plexus Block and Ultrasound

3.1. Introduction

Peripheral nerve block techniques (including brachial plexus block) have been performed since the early stages of the 20th century in patients needing upper extremity surgery, though the visualisation techniques have only recently been improved [28]. Identification of the brachial nerve bundle in a proper and secure way is very important for the successful injection of the local anaesthetic. Several techniques exist for the identification of the bundle: paresthesia technique with the use of anatomical landmarks, use of a nerve stimulator and more recently ultrasound guidance. The oldest one used is paresthesia, however it is accompanied with increased rates of several complications such as: failed block, vascular puncture/ damage or even temporary damage of the nerves. Improving on this technique comes the nerve stimulation, using inexpensive equipment and anatomical landmarks to locate the bundle, with better results both in terms of block success and in complication rates. However, this technique is still accompanied by a series of complications like increased patient discomfort, inability of the equipment performing the neurostimulation to identify the nerves and puncture of the neighbouring vasculature [29].

Ultrasound (U/S) guidance has demonstrated several advantages in comparison to the other techniques, and there is evidence that the use of ultrasound improves not only the quality of the block but also the speed of onset. The most important advantages are the following:

- 1) Direct visualization of the target neural bundle
- 2) Visualization of the neighboring vascular and other structures (bones, muscles)

- 3) Proper U/S needle guidance
- 4) Observation of the exact anatomical compartments that the local anesthetic spreads into
- 5) Decreased rate of complications such as: puncture and injection of the local anesthetic into the surrounding vasculature or intraneuronal, decreased rate of hemo-pneumothorax
- 6) Need for lower dosage of local anesthesia
- 7) Clear identification of anatomical variations

3.2 Technical considerations regarding the use of ultrasound

For the operator to harvest the plethora of advantages accompanying the use of ultrasound during a brachial plexus block, it is required to have adequate knowledge not only of the sonoanatomy but also of the basic ultrasound principles, while also regularly practicing. There are certain parameters that influence the imaging quality and thus the rate of block success. First of all, the frequency of the probe that will be used influences greatly the quality of the imaging, as higher frequency transducers produce detailed images of the more superficial anatomical structures, in the expense of lowering the depth of the penetration and thus making deeper structures (as is the case with the infraclavicular part of the brachial plexus) more difficult to differentiate [30]. Secondly, picking the correct needle size is important, as higher bore needles reflect ultrasounds better and thus make it easier for the operator to perform proper guidance of the needle. Thirdly, the angle of puncture and needle introduction is crucial for better imaging, with steeper angles making visualization harder [30].

3.3 Brachial plexus anatomy

The brachial plexus provides the upper extremities with both motor and sensory nerves. It originates between the 5th cervical (C5) and 1st thoracic (T1) spinal roots, and forms three trunks: the superior (C5 + C6 rami), the middle trunk (C7 ramus) and the inferior trunk (C8 + T1 rami). The trunks then pass through the interscalene groove, and they undergo separation into anterior (flexor) and posterior (extensor) divisions at the first rib (lateral border) [31]. Parts of those divisions further combine to form three cords: the lateral, the medial and the posterior cord. The anterior divisions of the superior and middle trunks combine to form the lateral cord, the posterior divisions of all three trunks join to create the posterior cord and the anterior division of the inferior trunk forms the medial cord. These cords further divide, giving rise to the terminal

branches of the brachial plexus, with each cord having at least two primary terminal branches:

- Lateral cord → musculocutaneous nerve and lateral portion of the median nerve.
- Posterior cord → radial and axillary nerves.
- Medial cord → ulnar nerve, medial portion of the median nerve and the intercostobrachial nerve (T2),

Additional nerves include:

- Lateral pectoral nerve (C5-C7) and medial pectoral nerve (C8-T1), (supplying the pectoral muscles)
- Long thoracic nerve (C5-C7), (supplying the serratus anterior muscle)
- Thoracodorsal nerve (C6-C8), (which supplies the latissimus dorsi muscle)
- Suprascapular nerve, (responsible for the supraspinatus and infraspinatus muscles)

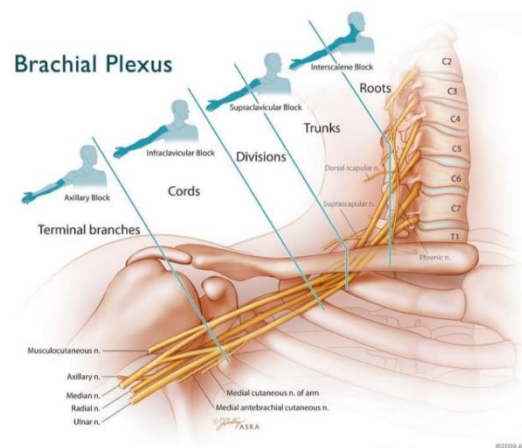


Figure 1: Brachial Plexus. Copyright 2009 American Society of Regional Anesthesia and Pain Medicine

4.0 Aim

This study is a systematic review of the literature and meta-analysis of studies comparing the outcomes of ultrasound guided regional anesthesia (brachial plexus block) versus local anesthesia during AVF construction in patients with chronic renal disease.

5.0 Methods

5.1 Literature search strategy

A comprehensive search of the literature was conducted to identify studies suitable for inclusion in this review and meta-analysis. The review was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [32] and the Cochrane Handbook for Systematic Reviews of Interventions [33]. The electronic search was conducted across three databases: PubMed, Scopus and Cochrane Library and was performed during September 2024. The search strategy included keywords, Title/Abstract terms [tiab] and Medical Subject Headings (MeSH) terms related to “Fistula”, “Brachial plexus block”, “Ultrasound” and “Regional anaesthesia”. A filter was applied to include studies published from 01/01/2000 until 01/09/2024, and to exclude non-English articles.

5.2 Eligibility criteria and study selection

This systematic review included all observational studies or controlled trials that reported the results of ultrasound guided regional anaesthesia (brachial plexus block) in patients with chronic renal disease (CRD), in need of hemodialysis, who underwent arteriovenous fistula creation. Non-English studies, animal studies, reviews, conference papers, expert opinions and case reports were excluded. Study selection was done in a two-step manner, first title and abstract screening for relevancy and then full text review for eligibility to this systematic review or the subsequent meta-analysis. The meta-analysis included comparative studies that divided CRD patients in need of fistula creation into two groups, group A (BPB) operated under brachial plexus block and group B (Local) operated under local anaesthesia with the prerequisite that they reported at least one of the following three surgical parameters:

- 1) Fistula patency at 3 months, which is the primary outcome of this systematic review and meta-analysis
- 2) Immediate fistula patency, which is a secondary outcome, or

3) Immediate Complications, which is also a secondary outcome

Fistula patency at 3 months was defined as the presence of blood flow in the fistula, 3 months after discharge from hospital, confirmed either with the use of U/S or by clinical examination (presence of bruit).

Immediate fistula patency was defined as the presence of blood flow in the fistula, at the time of discharge from hospital, confirmed either with the use of U/S or by clinical examination (presence of bruit).

Immediate complications were defined as presence of any type of surgical complications regarding the fistula, before the discharge from hospital, included but not limited to hematoma, hemorrhage, surgical site infection.

5.3 Data extraction

Data extraction was performed in a controlled manner and included but were not limited to: Study date and design, number of enrolled patients, demographics, type of anaesthesia, outcomes related to hemodynamic parameters or anatomy of the fistula, and early or late surgical outcomes. No results regarding different anaesthesia-related parameters were recorded due to inconsistency and non-standardization of result publication. The surgical outcomes that were included in the meta-analysis were: 1) Fistula patency at 3 months, which is the primary outcome of this systematic review and meta-analysis, 2) Immediate fistula patency, which is a secondary outcome, and 3) Immediate complications, which is also a secondary outcome.

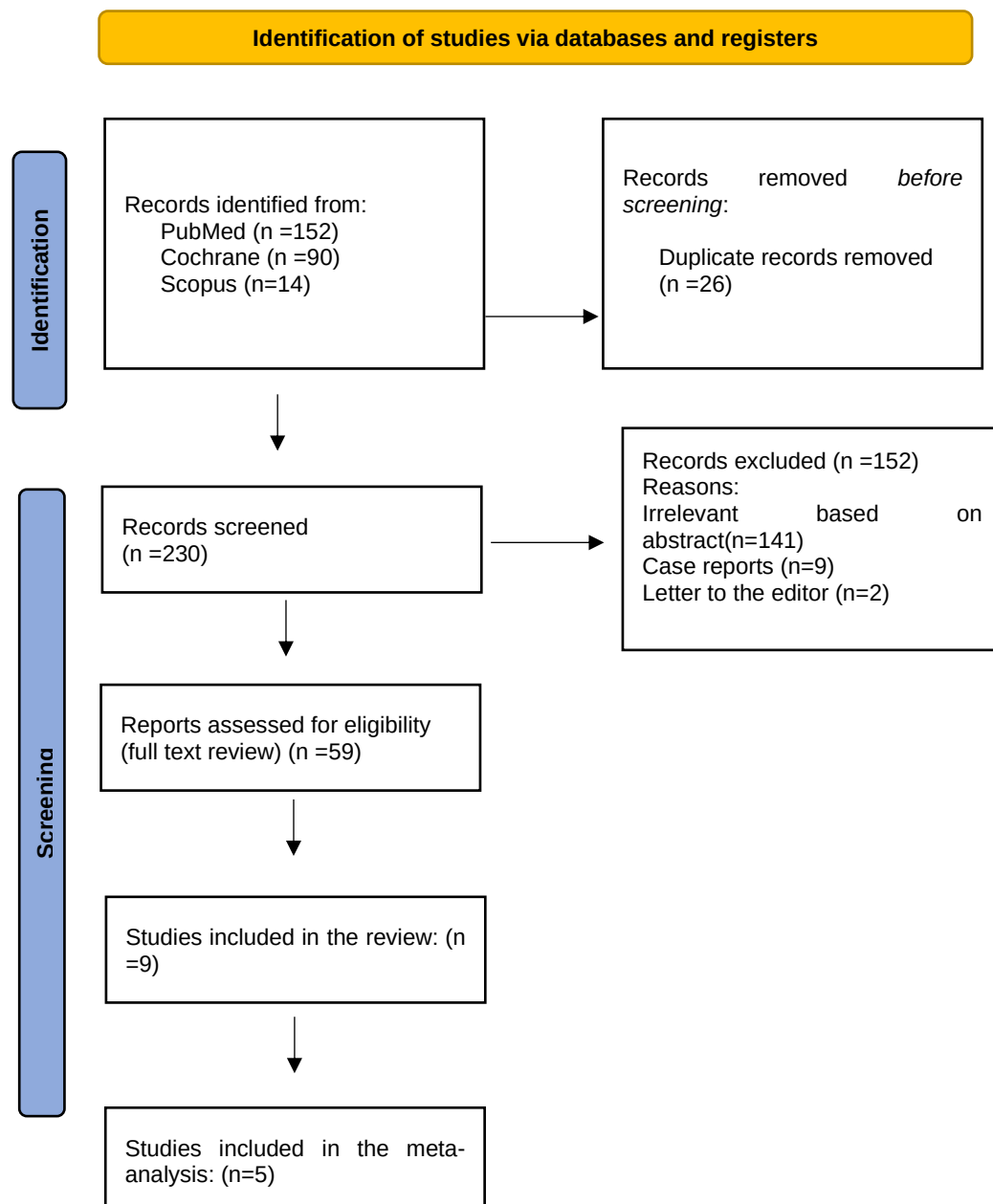
5.4 Meta-analysis

We used Review Manager software (RevMan version 5.4.1.) to analyze the extracted data using the Mantel-Haenszel method. Odds ratios (OR) were calculated with 95% confidence intervals (CIs) and were used as the outcome measure. P values were calculated and a value ≤ 0.05 was considered statistically significant. The analysis model included both the fixed effect, and the random effect models. Heterogeneity between ORs for the same outcomes across different studies were calculated using both the τ^2 and the I^2 inconsistency test, (a value of 0% indicates no statistical heterogeneity, while larger values signify more substantial heterogeneity). Funnel plots were created to assess publication bias. Sensitivity analyses were carried out in each outcome by excluding the most weighted study.

6.0 Results

6.1 Study Identification and PRISMA

The initial research resulted in 256 studies (152 from Pubmed, 14 from Scopus and 90 from Cochrane Library), and after removing 26 duplicate results, 230 studies were eligible for further review. From those studies, 152 were excluded after abstract review, for various reasons: 141 were irrelevant to the topic of this review (53 results from Cochrane, 2 from Spocus, and 86 from Pubmed), while 9 case reports (Pubmed) and 2 letters to the editor (Pubmed) were also excluded. Fifty-nine studies (59 from Pubmed and 19 from Cochrane) were eligible for full text review. Nine studies were included in this review (as shown on Table 1. -Appendix), while 5 of them were eligible for inclusion in the meta-analysis. The PRISMA flow diagram summarizes our search strategy:



6.2 Results -Systematic Review

In this systematic review of the literature 9 studies were included, with a total number of 896 patients enrolled. Five of those studies were randomized controlled trials, which were further analysed and included in the meta-analysis part of this study, as the other studies had no control group.

All patients included in those studies had chronic renal failure in need of haemodialysis and underwent a surgical fistula creation. In 6 of those studies two arms existed, one in which the patients were operated under U/S guided brachial plexus block (BPB), and a comparator arm in which the patients were operated under local anaesthesia. Out of these total 9 studies, 3 of them had no comparator arm, and all patients enrolled underwent BPB. One study with a comparator arm was not included in the meta-analysis as it reported the long-term results of an RCT that was already included, while all the other studies reported only short-term results.

A randomized controlled trial including 60 patients was published by Sahin et al. [13] in 2011 and it was a randomized controlled trial including 60 patients. They were randomly assigned in two groups, one that received infraclavicular BPB (n:30) and a control group (n:30) that received local anaesthesia. Measured at 3 hours, 7 days and 8 weeks postoperatively both the radial and the fistula blood flow were greater in the BPB group ($p < 0.001$). The primary patency was also greater in the BPB group (93% vs 83%), the primary failure rate was lower (7% vs 17%), and the early complication rate was lower (6.6% vs 16.6%) although none of these results reached statistical significance. No late complications or late failures were reported. These results were attributed to the significant vasodilation and sympathectomy-like effects produces by the brachial block [13].

During the same year, Lo Monte et al. [34], published another RCT, this time using U/S guided axillary plexus block vs local anaesthesia. Forty patients were randomized in two groups, each with 20 patients. To represent the extent of the sympathetic effect, the Pulsatility Index Ratio was used to express the change in the pulsatility index (PI), which was the ratio of the PI 10 minutes after the block and the one before. After BPB a 48.7% drop in the PI was observed, with a mean PI Ratio at 0.51, while at the local anaesthesia group it was calculated at 0.91. Basilic vein diameter was significantly greater after BPB (reporting a 26% average venodilation), with mean diameter before anaesthesia at 6.4 ± 2.25 mm and at the 10-minute interval 8.68 ± 2.95 mm, while in the local group the mean diameter before was 6.32 ± 2.7 mm and

after 10 minutes 6.6 ± 3.08 mm, resulting in a little to no venodilation. As far as early complications are concerned, no events were reported in the BPB group, while 20% complication rate was reported in the local group [34].

A third prospective study was published in 2011 by Reynolds et al. [35]. The study included 30 patients operated under U/S guided supraclavicular brachial plexus block and several parameters were examined. Average time for the block was 6 minutes, and all patients were successfully blockaded during the first 30 minutes. Change in the surgical plan was observed in 5 patients after BPB induced significant venodilation, favouring arteriovenous fistula creation over graft placement, and more distal located fistulas over proximal ones. An average vein diameter increases of 21.4% was reported ($p < 0.05$), favouring superficial over deep veins. Three fistula failures were reported and one seroma. At three months follow-up all fistulae had blood flow exceeding 600ml/min, and an average diameter increase of 0.33cm from post-block diameters [35].

In a prospective observational study from 2015 by Renaud et al. [36], 100 patients operated under U/S guided BPB (either supraclavicular, infraclavicular or axillary) were assigned into two groups based on preoperative mapping and whether there was a defined surgical plan for AVF creation (according to artery and vein size criteria) (Group A, n:41) or when the preoperative ultrasound was suboptimal and the plan was constructed after the use of BPB (Group B, n:59), or patients whose plan favoured a more distal AVF after significant vasodilatation. The study demonstrated a considerable AVF recruitment in those patients whose plan was modified or structured after the use of BPB, but the results did not differ significantly between the two groups in terms of hemodynamic and functional maturation, as well as one year primary and secondary patency [36].

Another study from 2015 published by Meena et al. [14], this time an RCT, included 60 patients, randomly divided into 2 groups, Group A (n:30) operated under U/S guided supraclavicular block and Group B (n: 30) operated under local anaesthesia. In all patients a radiocephalic AVF was created. Primary patency was 100% in group A, while 90% in group B ($p:0.24$). Other parameters that were included in the analysis were venous diameter, venous peak systolic velocity, venous blood flow and venous resistance index and all of them were significantly great in group A versus group B at several time points of measurement (30 minutes, 48hours, 2 weeks and 6 weeks post-operatively) ($p < 0.05$) [14].

A year later in 2016, an observer-blinded, RCT was published by Aitken et al. [11], comparing BPB (supraclavicular or axillary) versus local anaesthesia, while in 2020 the same research group published the long-term (one year) results of the original study along with a cost-effectiveness analysis [37]. The total number of 126 patients were randomly allocated to two groups, BPB group (n:63) and local anaesthesia group (n:63). The primary end point was primary patency at 3 months, which was significantly greater in the BPB group (84% vs 62% in the local group, $p<0.005$). Regarding immediate patency, BPB group was significantly better than local group (92% vs 73%, $p<0.005$), while functional patency at 3 months was reported at diminishing rates (41% at BPB group vs 29% at local group) and was not statistically significant. Concerning the long-term (1-year) results [37], primary patency of the BPB group was significantly greater (79% vs 59%, $p:0.008$). In total during those 12 months, 21 AVF revisions, 53 new AVFs and 50 temporary catheters were needed. Regional anaesthesia was also found to be cost-effective compared to local [37].

In 2017 Nofal et al. [12] published another RCT, this time using ultrasound guided axillary block. One hundred and forty patients were randomly split into two groups, group A (axillary block) and group B (local infiltration). Both in terms of mean radial artery blood flow and brachial artery diameter, group A demonstrated greater numbers, namely 3.52ml/min more artery blood flow and 0.68mm greater diameter, when compared to group B ($p<0.05$). Regarding AVF blood flow, group A demonstrated greater results at 4h, 1 week and 3 months post-operatively, with mean differences 29.6, 69.8 and 27.2ml/min respectively ($p<0.001$). Regarding the primary failure rate, although not statistically significant ($p=0.11$), the rate of group A was reported at 17% versus 30% of the primary failure rate of group B.

In conclusion, a prospective observational study published in 2018 by Palaniappan et al. [38], included 214 patients operated under ultrasound guided supraclavicular brachial plexus block. The researchers reported a 93.45% immediate patency, a 85.51% primary patency at 3 months and a functional patency of 47.19% at 3 months. In patients with brachiocephalic fistula the immediate patency was better at 96.24%, with a decline of functional patency at 3 months at 27.06%, while those with radiocephalic fistula although the reported immediate patency was lower, at 91.35%, the functional patency at 3 months was at 71.6%. Both the arterial and the venous diameters were increased, with the brachial and the radial artery to show an increase

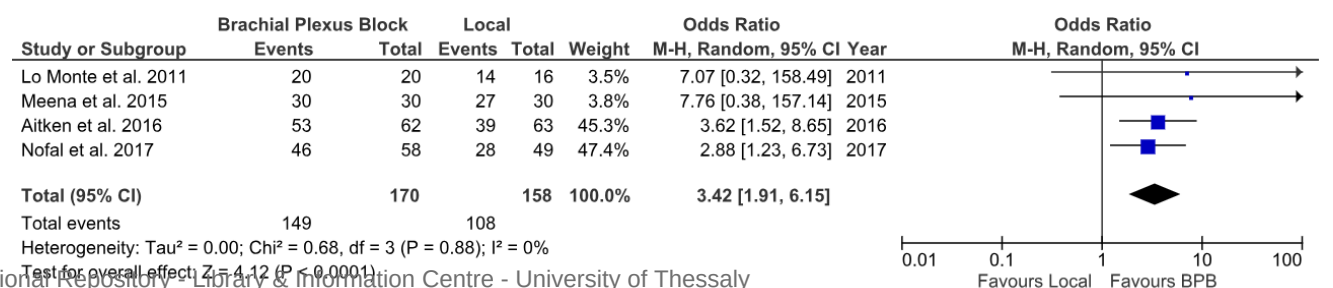
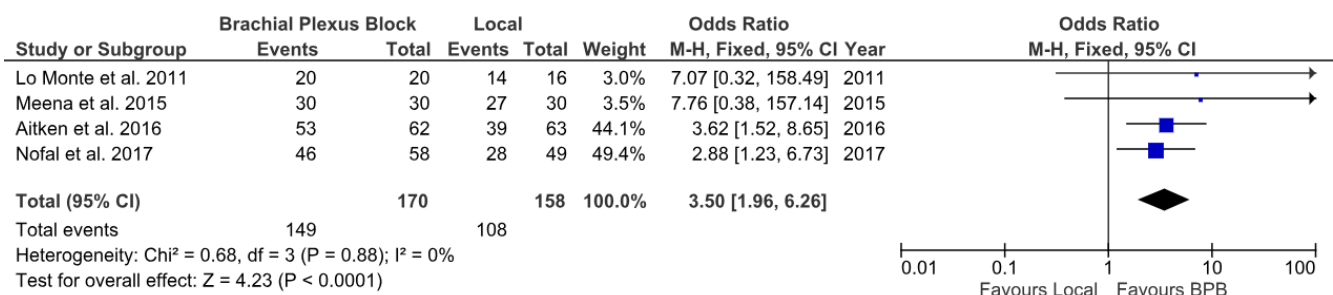
by 0.09mm and 0.08mm respectively ($p < 0.05$), and the cephalic vein an increase by 0.5mm ($p < 0.001$).

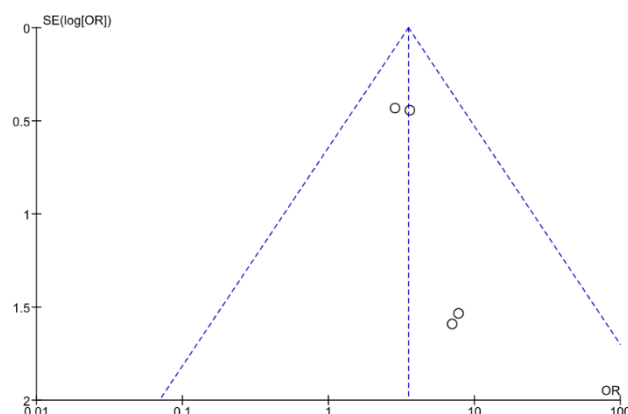
6.3 Results of the meta-analysis

Five randomized controlled trials were analysed (as shown on Table 2. - Appendix), including patients operated under brachial plexus block or local anaesthesia during upper limb arteriovenous fistula creation. Three surgical outcomes were included: Fistula patency at 3 months post-operatively (primary outcome), immediate fistula patency and immediate complications (secondary outcomes). The analysis was carried out using the odds ratio as the outcome measure and both a fixed and a random-effects model was fitted to the data. The amount of heterogeneity was estimated using both the τ^2 and the I^2 statistic. Funnel plots were created to check for publication bias. Sensitivity analyses in each outcome were carried out by excluding the most weighted study.

6.3.1 Fistula patency at 3 months – Primary outcome

A total of $k=4$ studies were included in the analysis. The observed odds ratios ranged from 2.88 to 7.76. The estimated average odds ratio based on the fixed-effects model was 3.50 (95% CI: 1.96 to 6.26), while based on the random-effects model was 3.42 (95% CI: 1.91 to 6.15), therefore, the average outcome differed significantly from one ($p < 0.0001$). According to the τ^2 and the I^2 , there was no significant amount of heterogeneity in the true outcomes ($\tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.88$). According to the test for overall effect, the results appear to be statistically significant ($p < 0.0001$). The rank correlation test did not indicate any funnel plot asymmetry, and thus did not detect any publication bias.





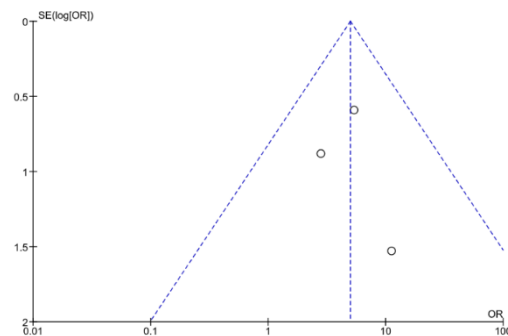
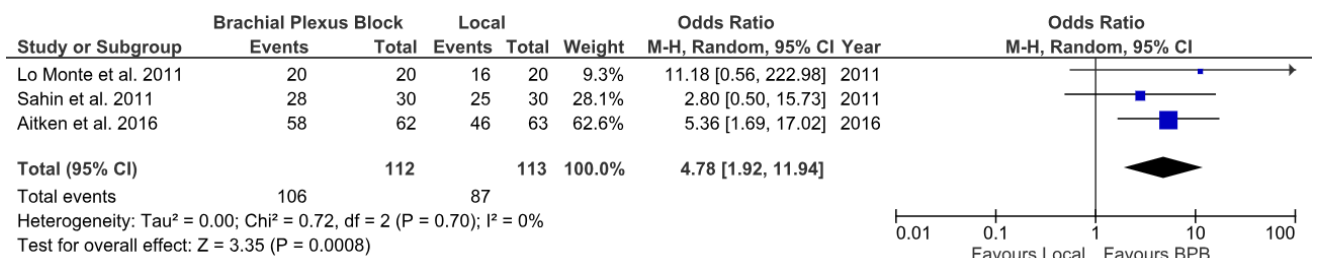
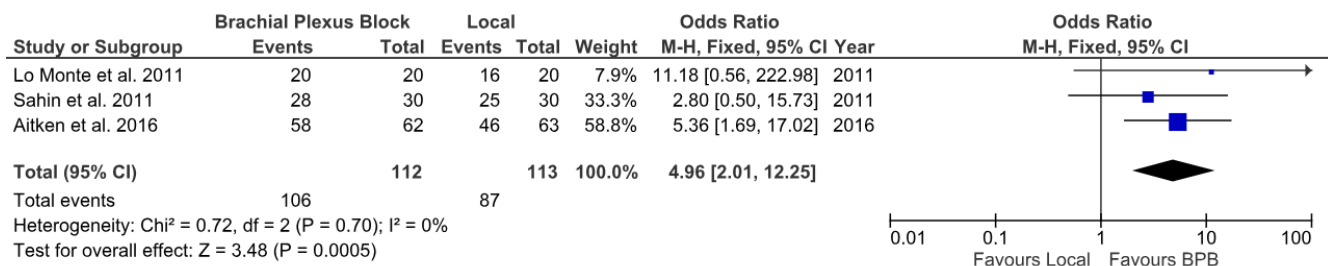
Two groups of patients were compared, at 3 months post-operatively, with group A being the pool of patients operated under brachial plexus block (n:170), and group B being those patients operated under local anaesthesia (n:158). Group A had 21 events of fistula failure in 3 months, while group B had 50 events of failure. The odds ratio of fistula patency ranged from 3.42 to 3.5, without the inclusion of one within its 95% confidence intervals, which demonstrates that patients operated under brachial plexus block had 3,5 times better chances of a patent fistula at 3 months postoperatively versus those operated under local anaesthesia ($p < 0.0001$).

A sensitivity analysis was performed by removing the most-weighted study by Nofal et al. [12]. In the fixed effect model the result was still statistically significant (OR 4.11, 95%CI 1.84-9.17, $p = 0.0005$), while also retaining the statistical significance in the random effect model (OR 4.00, 95%CI 1.79-8.98, $p = 0.0008$). Further removing the second most weighted study by Aitken et al [11] did not result in any statistically significant outcomes (fixed effect: OR 7.44 95%CI 0.85-64.82, $p = 0.07$ and random effect: OR 7.42 95%CI 0.85-64.47, $p = 0.07$).

6.3.2 Immediate fistula patency – secondary outcome

A total of $k=3$ studies were included in the analysis. The observed odds ratios ranged from 2.80 to 11.18. The estimated average odds ratio based on the fixed-effects model was 4.96 (95% CI: 2.01 to 12.25), while based on the random-effects model was 4.78 (95% CI: 1.92 to 11.94), therefore, the average outcome differed significantly from one ($p < 0.001$). According to the τ^2 and the I^2 , there was no significant amount of heterogeneity in the true outcomes ($\tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.7$). According to the test for overall effect, the results appear to be statistically significant ($p < 0.001$). The

rank correlation test did not indicate any funnel plot asymmetry, and thus did not detect any publication bias.

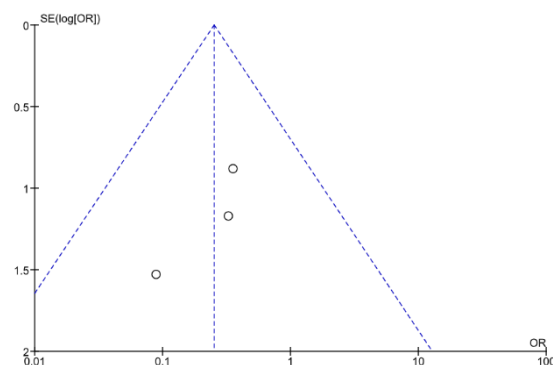
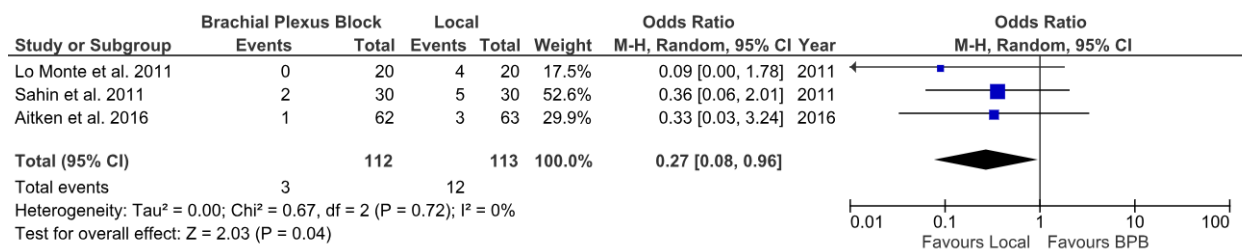
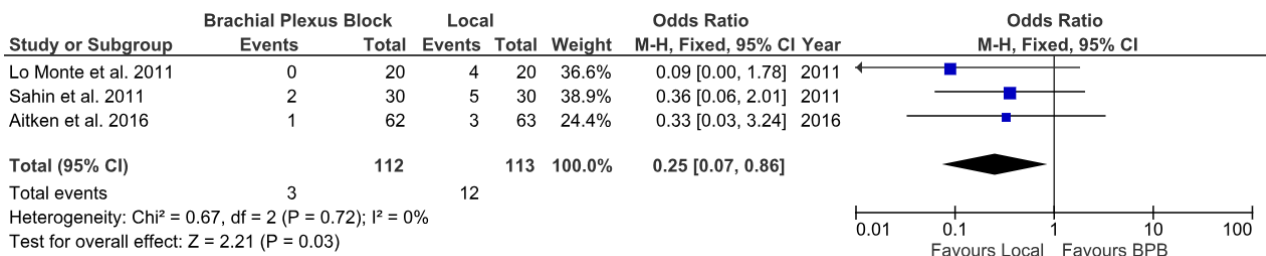


Two groups of patients were compared, with group A being the pool of patients operated under brachial plexus block (n:112), and group B being those patients operated under local anaesthesia (n:113). Group A had 6 events of immediate fistula failure, while group B had 26 events of immediate failure. The odds ratio ranges from 4.78 to 4.96, without the inclusion of one within its 95% confidence intervals, which demonstrates that patients operated under brachial plexus block had an average of 4.8 times better chances of a patent fistula at discharge versus those operated under local anaesthesia ($p < 0.0001$).

A sensitivity analysis was performed by removing the most-weighted study by Aitken et al. [11]. In the fixed effect model the result was still statistically significant (OR 4.4, 95%CI 1.03-18.74, $p = 0.05$), while in the random effect model statistical significance was not achieved (OR 3.96, 95%CI 0.89-19.85, $p = 0.07$).

6.3.3 Immediate complications – secondary outcome

A total of k=3 studies were included in the analysis. The observed odds ratios ranged from 0.09 to 0.36. The estimated average odds ratio based on the fixed-effects model was 0.25 (95% CI: 0.07 to 0.86), while based on the random-effects model was 0.27 (95% CI: 0.08 to 0.96), therefore, the average outcome differed significantly from one ($p < 0.001$). According to the τ^2 and the I^2 , there was no significant amount of heterogeneity in the true outcomes ($\tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.72$). According to the test for overall effect, the results appear to be statistically significant ($p < 0.05$). The rank correlation test did not indicate any funnel plot asymmetry, and thus did not detect any publication bias.



Two groups of patients were compared, with group A being the pool of patients operated under brachial plexus block (n:112), and group B being those patients operated under local anaesthesia (n:113). Group A had 3 events of immediate complications, while group B had 12 events of immediate complications. The odds ratio ranges from

0.25 to 0.27, without the inclusion of one within its 95% confidence intervals, which demonstrates that patients operated under brachial plexus block had an average of 4 times less chance of an immediate postoperatively complication versus those operated under local anaesthesia ($p < 0.0001$).

A sensitivity analysis by removing the most-weighted study by Sahin et al. [13] did not result any statistically significant results with either model [fixed (OR 0.18, CI 0.03-1.09, $p = 0.06$) or random effect (OR 0.20, CI 0.03-1.25, $p = 0.09$)].

7.0 Discussion

This systematic review included 9 studies, with a total number of 896 patients and the pooled analysis included 5 RCTs with a total number of 426 enrolled patients. All studies included were published after the year 2010, and thus incorporate newer techniques, both in terms of fistula creation and in application of the brachial plexus block, namely the use of ultrasound guidance. This is the first meta-analysis to not only include but also focus on all the randomized controlled trials published after 2000, regarding brachial plexus block versus local anaesthesia for fistula creation, that also concentrates on certain surgical outcomes: fistula patency at 3months, immediate fistula patency, and immediate complications.

Regarding the 3 months patency, not only did each individual study included [11,12,14,34] report superior results in the BPB group versus the local anaesthesia group, but also the pooled analysis demonstrated an OR 3.50 which was statistically significant (95% CI: 1.96 to 6.26, $p < 0.0001$), and retained its significance in the sensitivity analysis even after removing the more weighted study by Nofal et al. [12] (OR 4.11, 95%CI 1.84-9.17, $p = 0.0005$). At 3 months follow-up Reynolds et al. reported that all patients operated under BPB with patent fistulae had also blood flow exciding 600ml/min, and an average diameter increase of 0.33cm from post-block diameters [35]. Aitken et al. regarding 1-year post-operative results found that, primary patency of the BPB group was significantly greater (79% vs 59%, $p = 0.008$), and that BPB was also cost-effective [37]. On the other hand, Renaud et al. reported that the results did not differ significantly between the two groups in terms of hemodynamic and functional maturation, as well as one year primary and secondary patency [36]. Primary patency does not always necessitate functional patency (which is the goal of the surgical operation), as is the case with Palaniappan et al. [38] who included 214 patients operated under ultrasound guided supraclavicular brachial plexus block and reported

an 85.51% primary patency at 3 months but a drop in functional patency at 47.19%. Follow-up for a longer period is necessary to safely interpret those results though, as in some cases more than 3 months are needed for the maturation and use of the fistula during hemodialysis, or in other cases a supplementary operation is required (for example superficialization) to safely access the vessels.

Regarding immediate patency 3 RCTs were included [11,13,34], with the results of the pooled analysis showing that patients operated under BPB had almost 5 times better outcome versus the control group [OR 4.96 (95% CI: 2.01 to 12.25), $p < 0.05$] and although most of the weight 58,8% is on one study by Aitken et al [11], sensitivity analysis done by removing this study, resulted again in statistically significant results (OR 4.4, 95%CI 1.03-18.74, $p = 0.05$). This effect can probably be attributed to the sympathetic blockade caused by regional anaesthesia and the subsequent increase in fistula blood flow [13]. Lehtipalo et al. [39] reported that interscalene BPB reduces sympathetic nervous activity, resulting in increased skin blood flow and temperature, and a reduction in vessel constriction. Ebert et al. reported that the average arterial and venous flows were increased by 1.9 and 8.6 times, respectively, after BPB [40], while Sahin et al. [13] reported a 1.5-fold increase in radial artery flow after BPB.

Concerning immediate surgical complications, 3 RCTs were included and the results of the analysis demonstrated a 4-fold decrease in immediate post-operative complications in the BPB group: OR 0.25 (95% CI: 0.07 to 0.86, $p = 0.03$), although more data are needed to generalize this result, as the number of patients included ($n = 225$) was relatively small and after sensitivity analysis the outcome was not statistically significant (OR 0.18, CI 0.03-1.09, $p = 0.06$).

Ultrasound-guided neural blockades are generally considered safe during operations of the upper extremities, and Nofal et al. reported that ultrasound-guided BPBs, when performed by an experienced anesthesiologist, are both safe and effective in providing adequate anesthesia during vascular operations [12]. Despite the advantages of the brachial plexus block in several aspects of fistula creation, inexperience in performing the different techniques or in the use of ultrasound can lead to serious complications. Inaccurate injection of the anaesthetic can lead to systemic toxicity due to intravascular administration [41], or even local vascular complications like hematoma, edema, or even ischemia [15]. Intra-neural injections may cause lasting paresthesia or even paralysis of the arm [15]. Depending on the type of BPB, both the

supraclavicular and the interscalene approaches have been associated with increased risk of Horner's syndrome and pneumothorax [42].

Three other systematic reviews and meta-analysis exist regarding the same comparison as this one, each focusing on a different endpoint and with slight variations on the number of studies included [43,44,45].

The earlier published study by Cerneviciute et al. (2017) [43] included 4 RCTs in the pooled analysis while not including the RCT by Nofal et al. [12] which was published the same year. The primary end point of that meta-analysis was the fistula failure rate, while no secondary end points existed. The researchers concluded that there was a lower failure rate between patients operated under regional anaesthesia compared to local, and that was statistically significant even after excluding the most heavily weighted study [OR 0.28, 95% CI 0.14-0.57, $p=0.0005$) and (OR 0.20, 95% CI 0.05-0.75, $p=0.02$), respectively] [43].

At the same year (2017) the next meta-analysis was published by Ismail et al. [44], including 6 RCTs and one retrospective study. As was also the case with the study from Cerneviciute et al. [43], the newest RCT available by Nofal et al. [12] was not included. Instead, an RCT by Mouquet et al. [46] was included, which was published in 1989 and assigned the patients in 4 groups with 9 patients each, one group with BPB, one local and 2 groups with general anaesthesia, each with different choice of anaesthetics. Apart from the heterogeneous types of anaesthesia, different types of vascular access also took place, as in 5 patients a graft was placed. Ismal et al. concluded that BPB outweighed local anaesthesia in terms of fistula blood flow, brachial artery diameter and blood flow, and outflow vein diameter, while no statistically significant results could be drawn regarding all post-operative and anesthetic complications or fistula thrombosis rate.

The later pooled analysis published by Gao et al. [45] (2020) included 8 studies, 7 RCTs and one retrospective study which in the pooled analysis was the study that weighed the most. Out of the 7 RCTs, 5 were the same studies included also in this study, while the others were the study by Mouquet et al. [46], which methodologically lacks the focus of comparing BPB versus local for AVF creation, and the other one was by Shoshiashvili et al. [47], a study that focused only on reporting anaesthesiology related outcomes and not surgical ones. Gao et al. reported that regional anaesthesia was associated with significantly better primary patency rates than local (OR, 1.88; 95% CI: 1.24–2.84; $P = 0.003$, $I^2=31\%$) and increased brachial artery diameters (mean

difference (MD), 0.83; 95% CI: 0.75–0.92; $P < 0.001$; $I^2 = 97\%$), while local anaesthesia was associated with reduced brachial artery blood flow (MD, 47.5; 95% CI: 35.18–59.12; $P < 0.001$; $I^2 = 83\%$) and shorter operative times (MD, – 29.63 min, 95% CI: – 32.78 - -26.48; $p < 0.001$; $I^2 = 100\%$). While those results are statistically significant, they derive from studies with great heterogeneity. Regarding patency rates, no long-term outcomes were included.

In summary, this systematic review and meta-analysis suggests that ultrasound-guided brachial plexus blocks in patients with late-stage renal disease operated for a fistula construction have several advantages compared to local anaesthesia. In terms of fistula patency at 3 months post-operatively, immediate fistula patency and immediate complications, brachial plexus blocks demonstrate a statistically significant benefit in contrast to local anaesthesia. Nevertheless, more well-constructed RCTs, with longer follow-up periods, are required to support the everyday use of U/S guided BPB in clinical practice.

8.0 Limitations

The limitations of the present pooled analysis reflect the limitations posed by the studies included and although it includes only RCTs, the results should be interpreted cautiously. First, the small number of included studies (5), despite the low in-between heterogeneity, as well as the relatively small number of included patients (426), increase the risk of inherent bias. Second, brachial plexus block can be performed with several approaches: supraclavicular, infraclavicular, axillary and interscalene. We included studies using different techniques for the block, (although all were done under ultrasound guidance) while also using different types, volumes and concentrations of anesthetic drug administered to patients. Third, only short-term outcomes are available in literature, and this creates the need for several other future studies, namely more well-designed RCTs or even the creation of a dedicated registry, to explore the long-term outcomes of these types of procedures.

9.0 Conclusion

In patients with end-stage renal disease, operated for arteriovenous fistula creation, ultrasound-guided brachial plexus block when compared with local anesthesia, appears to lead to higher patency rates, both at the immediate post-operative period and at 3 months, as well as lower surgical complications.

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11.0 Appendix:

Table 1. Studies including patients operated under U/S guided brachial plexus block and their most important findings

First Author	Year	Type of Anesthesia	Number of Patients	Findings
Sahin [13]	2011	U/S Guided Infraclavicular BPB vs Local	60 (RCT)	BPB increased arterial and AVF blood flow at 3 hours, 7 days, and 8 weeks post-operatively.
Lo Monte [34]	2011	U/S Guided Axillary BPB vs Local	40 (RCT)	BPB increased vein diameter and reduced pulsatility index (PI)
Reynolds [35]	2011	U/S Guided Supraclavicular BPB	30	BPB increased vein diameter
Renaud [36]	2015	U/S Guided Supraclavicular/Infraclavicular/Axillary BPB	100	Increased recruitment for AVF creation without improved long-term outcomes regarding patency.
Meena [14]	2015	U/S Guided Supraclavicular BPB vs Local	60 (RCT)	BPB resulted in improved hemodynamic parameters, BPB group 100% patency – local group 90% patency, though non-significant difference.
Aitken [11]	2016	U/S Guided Supraclavicular/Axillary BPB vs Local	126 (RCT)	BPB improved patency at 3 months.
Nofal [12]	2017	U/S Guided Axillary BPB vs Local	140 (RCT)	BPB with significantly greater arterial and AVF blood flow.
Palaniappan [38]	2018	U/S Guided Supraclavicular BPB	214	BPB increased vein diameter and patency rate immediate postoperatively and at 3 months.
Aitken [37]	2020	U/S Guided Supraclavicular/Axillary BPB vs Local	126	BPB leads to significant improvement in primary and functional patency at 12 months and is cost-effective

U/S: Ultrasound, BPB: Brachial Plexus Block, RCT: Randomized Control Trial,
AVF: Arteriovenous Fistula

Table 2. Studies included in the meta-analysis

STUDY- OUTCOME	Immediate Patency (number of patients BPB - Local)	Patency at 3 months (number of patients BPB - Local)	Immediate complications (number of patients BPB - Local)
Sahin [13]	28/30 – 25/30 (93.3% - 83.3%)	-	2/30 – 5/30 (6.66% - 16.6%)
Lo Monte [34]	20/20 – 16/20 (100% - 80%)	20/20 – 14/16 (100% - 87.5%)	0/20 – 4/20 (0% - 20%)
Aitken [11]	58/62 – 46/63 (93.5% - 73%)	53/62 – 39/63 (85.5% - 61.9%)	1/62 – 3/63 (1.61% - 4.76%)
Meena [14]	-	30/30 – 27/30 (100% - 90%)	-
Nofal [12]	-	46/58 – 28/49 (79.3% - 57.1%)	-

BPB: Brachial Plexus Block