The efficacy of the Cook-Swartz implantable Doppler in the detection of free flap compromise: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004253
Article Type:	Protocol
Date Submitted by the Author:	15-Oct-2013

Complete List of Authors:	Agha, Riaz; Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK, Plastic Surgery department Gundogan, Buket; University College London Medical School, London,UK, Fowler, Alexander; Barts and the London School of medicine and dentistry, Bragg, Thomas; Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK, Plastic Surgery department Orgill, Dennis; Brigham and Women's Hospital, Boston,, Division of Plastic Surgery

Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice, Surgery, Ear, nose and throat/otolaryngology
Keywords:	SURGERY, Plastic & reconstructive surgery < SURGERY, Otolaryngology < SURGERY, Head & neck surgery < SURGERY

The efficacy of the Cook-Swartz implantable Doppler in the detection of free flap compromise: A systematic review protocol

REVIEW INFORMATION

Authors: Riaz A. Agha[a], Buket Gundogan[b], Alexander J. Fowler[c], Thomas WH Bragg[a], Dennis P. Orgill[d]

Contact person: Buket Gundogan (buket.gundogan.11@ucl.ac.uk)

Institutions: a – Department of Plastic Surgery, Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK

b – University College London Medical School, London,UK

c – Barts and the London School of Medicine and Dentistry, QMUL, London, UK

d – Division of Plastic Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA

ABSTRACT

Introduction

The Cook-Swartz implantable Doppler monitors venous blood flow from free flaps and can detect post-surgical free flap compromise. Previous studies have shown that the use of this Doppler can improve detection and salvage rates as it provides an earlier warning than the current method of clinical assessment. Such studies assert that the implantable Doppler is of great value in monitoring of free flaps in current microsurgical units. This systematic review aims to compare the efficacy of the Cook-Swartz implantable Doppler in monitoring free flap compromise against conventional clinical free flap monitoring techniques such as flap capillary refill or blanching time, skin temperature, turgor and flap skin colour.

Methods and analysis

Various electronic databases will be systematically searched for studies which compare the use of Cook-Swartz implantable Doppler with clinical assessment in detecting the failure of free flaps. The selected studies will then have their titles and abstracts screened by two authors and any conflicts not resolvable between the two authors will be referred to the lead author for resolution. Articles selected after title and abstract screen will have full text downloaded and the complete article will be assessed for suitability. Once articles have been selected for inclusion, data extraction will take place. For the data analysis, the outcomes of the studies will be tabulated, with descriptive statistics performed as appropriate and the detection rate of the

Doppler and clinical assessment will be compared and synthesised where possible.

Ethics and Dissemination

The authors hope to disseminate the findings as widely as possible, irrespective of results as it will help to increase the knowledge base on monitoring techniques of free flaps. This systematic review will be published in a peer-reviewed journal and include a number of recommendations as its conclusion based upon the evidence contained within. Given the wide range of specialities now utilising flaps, it will be presented at a wide range of national and international conferences.

Protocol Registration: CRD42013005818

BACKGROUND

Free flap reconstruction

Free flap reconstruction for large tissue defects is increasingly common and plays an important role in the field of plastic and reconstructive surgery.[1] Such surgery necessitates a microsurgical anastamosis from the harvested flap to the recipient using minute sutures. Data suggests that the commonest cause of failure is a problem with the venous anastamosis occurring within the first 24 to 48 hours postoperatively.[2,3, 4] This problem affects up to 20% of all free flap reconstructions, depending upon their location and entails significant physical, psychological and emotional morbidity for patients.[5, 6 7]

Flap failure often necessitates further general anaesthetics and operations. Due to the time critical nature of flap failure, reoperation may occur out of hours, which provides further logistical and practical challenges.[7] Initially, an attempt is made to salvage the flap, if this fails, then the flap is removed and an alternative reconstructive approach may be required. In some cases, venous congestion may require blood drainage; for example by use of medicinal leeches.[8] This is potentially highly unpleasant for patients and predisposes them to infection and anaemia.[9] Patients therefore require careful wound inspection, surveillance of haemoglobin and prophylactic antibiotics to protect them from further complications.[8, 10]

Monitoring of free flaps

Early recognition of flap compromise is the primary aim of every microsurgical unit. Prompt intervention and rescue is critical for ensuring flap survival.

However, the complexities of free flap microcirculation are often difficult to assess.[11] At present, monitoring is carried out clinically and is based upon subjective clinical observations. These tests are carried out on an island of skin or 'skin paddle' – an area of skin considered to be indicative of the whole flap's arterial perfusion and venous drainage.[12] Such tests may include the colour, capillary refill or blanching time, skin temperature, turgor, and degree of bleeding in response to pin-prink and use of a handheld doppler device.[1]

Unlike solid organ transplantation, there is no objective assessment - such as decreased urine output in renal transplantation. Similarly, there are currently no suitable imaging modalities for assessing microvascular flow and specifically slow venous flow problems, though there are reports in the literature of the use of nuclear medicine techniques in successful monitoring.[13] A number of small studies have highlighted the use of Single-Positron Emission Computed Tomography (SPECT) in the determination of free flap compromise.[14] However, large comparative studies are required with standardised techniques to further define the role of this modality in the assessment of free flap compromise. Early compromise, which entails the large majority of flap failure, is often asymptomatic. Pain, bleeding and skin changes can take a while to develop, potentially increasing ischaemic times and reducing the possibility of successful salvage.[15]

Some free flaps are very challenging to monitor adequately, such as vascularised bone and muscle flaps; especially those that have been covered with a skin graft and cutaneous flaps in non-Caucasian skin. Some flaps, such as buried flaps within the head and neck are impossible to monitor by visual, clinical assessment and in such circumstances, attempts have been made to enhance clinical monitoring using microdialysis.[11, 16] However, this can take up to 30 minutes to get a reading, necessitates training to learn a technique and analyse results, does not directly measure flow and costs almost $52,000 per monitor plus additional costs of up to $570 per flap.[11]

The Cook-Swartz Implantable Doppler

The Cook-Swartz implantable Doppler monitors the venous flow from free flaps and obtained its CE mark in 2006.[17] Since then it has been distributed widely in both Europe and the rest of the world.[17] It is the only device currently on the market that allows this monitoring and is protected by patent. It consists of a 20 MHz ultrasonic Doppler crystal, a silicone cuff and a monitor unit.[18, 19] This cuff secures the Doppler to the flap's vein at the time of the operation and is placed downstream of the microvascular anastamosis.[19] The Doppler provides monitoring for 5-10 days postoperatively and is removed by simple traction.[17] A number of studies have shown that use of this device increases success and salvage rates as it provides an earlier warning that the current method of clinical monitoring.[12, 20-22]

The potential of the Cook-Swartz Doppler

The use of the Cook-Swartz Doppler in the assessment of such flaps has demonstrated improved detection times.[2, 12, 20, 22, 23] This technology is needed now more than ever as the indications for, and therefore absolute number of, free flaps have increased. Indications for flaps include following resection of breast tumours, head and neck cancers, skin cancers, major burns and infections. Often these may be 'cross-speciality' flaps, for example with orthopaedics to cover exposed metal work in lower limb fractures. Changes to working practices mean that these patients may be returned to an orthopaedic or general surgical ward where monitoring is performed by non-specialist nurses who may not be used to monitoring flaps, let alone over night and in challenging settings such as low light.

Why is a systematic review of this required?

To our knowledge, there has only been one systematic review involving the Cook-Swartz Implantable Doppler. Poder and Fortier investigated the efficacy and cost effectiveness of the implantable Doppler.[24] However, we aim to investigate and further clarify the role of the Doppler as a monitoring technique by comparing it to clinical assessment. Clinical assessment is the most widely used technique and as such the standard against which the Doppler should be compared. Further clarifying the role and possible benefit of the Cook-Swartz Doppler in the detection of free flap compromise would allow modification of practice and guidelines in line with the best evidence.

OBJECTIVES

Our objective is to perform a comprehensive systematic review of the implantable Doppler in the detection of free flap compromise.

Primary objective:

To compare the efficacy of the Cook-Swartz implantable Doppler versus clinical assessment in the detection of free flap compromise.

Secondary objectives:

To determine the absolute indications for use of the Doppler if any. Quanitfy the false positive and negative rates, salvage rates and number of associated complications.

METHODS

This systematic review will be conducted according to the recommendations outlined in the Cochrane Handbook for reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25]

Criteria for selecting studies:

The following search criteria were specifically devised to locate studies specifically pertaining to the use of the Cook-Swartz Doppler and to provide evidence for the objectives previously stated.

Types of studies

Any study comparing the use of Cook-Swartz implantable doppler with clinical assessment in detecting the failure of free flaps will be included. Articles must describe use of the implantable doppler specifically and may be of any grade of evidence (1 to 5 as defined by the Oxford Centre for Evidence-Based Medicine).[26]

Any article where data is duplicated will be excluded, as will articles not describing original data; such as editorials, letters regarding other articles and discussion pieces. Unpublished reports will be included if the methodology and results are accessible in written form.

Types of participants

Human subjects of any age who have undergone free flap surgery. There will be no limitation on location of the flap or technique utilised.

Types of interventions

Any article describing use of the Cook-Swartz Doppler in the detection of free flap compromise would be considered. Ideally, this would be considered against a control group of clinical monitoring.

Types of comparator

Cook-Swartz implantable Doppler used on the venous pedicle of a free flap attached by any means and used to monitor free flaps post-operatively. Clinical assessment of free flaps including, but not limited to; skin colour, turgor, surface temperature, capillary refill time or handheld Doppler.

Types of outcome measures

Primary outcome:

The rate of detection will be determined as the number of Doppler monitored flaps correctly identified as compromised divided by the total number of Doppler monitored flaps. This will be compared with clinical monitoring.

Secondary outcomes:

The salvage rate will be the number of compromised flaps successfully salvaged divided by the total number of compromised flaps. The false positive rate is the number of flaps monitored by Doppler returned to theatre incorrectly divided by the total number of Doppler monitored flaps.

The false negative rate will be the number of flaps lost without any change in Doppler monitoring, divided by the total number of Doppler monitored flaps.

The true negative rates will be the number of flaps monitored without any change in Doppler and without any compromise divided by the total number of Doppler monitored flaps.

The rates for clinical assessment will be calculated as above and compared to that of the Doppler.

Search methods for identification of studies

Electronic Searches

The following electronic databases will be searched to 24th September 2013: PubMed, EMBASE, PsycINFO, Ebosco, Cochrane Database of Systematic Reviews, CINAHL, SCOPUS, SciELO, NHS evidence, www.uptodate.com, http://clinicaltrials.gov/, http://www.who.int/ictrp/en/, http://www.controlled-trials.com/

Search terms and keywords

The search strategy has been developed to locate papers related specifically to the Cook-Swartz implantable Doppler. This search will utilise the English language keywords combined with Boolean logical operators. Therefore the following terms will be utilised: "*Implantable doppler*" OR *"Cook-Swartz implantable doppler"* OR "*Cook-Swartz Implantable doppler*".

The search will not be limited by language. Any non-English articles identified will proceed to title and abstract screening and the full text obtained if required. If full text is not available, then the authors will be contacted to obtain an English language copy of the full text. Failing this, colleagues speaking the language will be contacted to translate. Google Translate will be utilised as a last resort.

Other resources

A hand search of the references of articles located by the search strategy will be used to identify any relevant citations within the grey literature. Active researchers will be contacted to identify any other published or unpublished work.

Identification and Selection of articles

Studies identified by the electronic and manual search strategy will be listed. Results including citation, title and abstracts will be populated into EndNote®

(Thomson Reuters, New York, NY, USA) and duplicates removed. Titles and abstracts will be screened by two authors (BG and AJF), any conflicts not resolvable between the two will be referred to the lead author (RA) for resolution. Articles selected after title and abstract screen will have full text downloaded and a further assessment made. Once articles have been selected for inclusion, data extraction will take place.

Data extraction and management

Data will be extracted independently by two authors (BG and AJF) utilising a standard extraction form where all data for each study will be collated (Appendix A). Any conflict of extraction will be resolved by discussion; where resolution this isn't possible, the lead author (RA) will have final say. This data will then be entered into a Microsoft Excel ® 2011 database (Microsoft, Redmond, WA, USA). Data collected will constitute three main areas:

1) **Article information**
   - Title
   - Authors
   - PubMed ID
   - Year of publication
   - Journal
2) **Characteristics**
   - Setting and Location of the study
   - Number of patients
   - Range of patient age
   - Flap types included

- Clinical method of assessment
- Doppler method of assessment

3) **Results (divided clinical and doppler)**

- Number of patients per group
- Specific flaps in groups (where applicable)
- Detected
- Flap Salvage
- Needless theatre return
- Complications
- Lost flaps without any signs
- Flaps correctly monitored

Assessment of study quality and bias in included studies

The quality of evidence included in this analysis needs to be established. Quality of evidence can be assessed based upon a number of criteria; we will be specifically utilising the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system as proposed by Balshem et al.[27]

If we locate any Randomised Controlled Trials (RCTs) we will utilise the Cochrane risk of bias tool and compare outcomes to published trial protocols. Any information missing from studies will be documented and assessed to ascertain the risk of incomplete statistical sets.

Assessment of publication bias

To ascertain if studies with negative outcomes are not being published ("publication bias"), we will assess funnel plot asymmetry.[28, 29] Where both positive and negative results are published, the plot should resemble a symmetrical, inverted funnel. The prevision of the estimated intervention effect will increase as the size of the sample included in the study increases. Smaller studies will therefore scatter widely at the bottom, with larger, more powerful studies grouping more narrowly at the top. The asymmetrical distribution of standard error on analysis of the funnel plot would indicate publication bias.

Assessment of Heterogeneity

Heterogeneity between studies will be assessed using Higgins and Thompson's I^2, which measures the percentage variability in result attributable to heterogeneity between studies rather than sampling error[28]. Variability in the intervention effects in studies will be tested for statistical heterogeneity utilising Tau-squared (T^2), I^2 and chi-squared (X^2) with corresponding P-values calculated; the Cochrane tests.

The value of X^2 statistics in the forest plot presents the assessment of whether the differences in results are compatible with chance alone. A large value of X^2 test relative to its degree of freedom (df) or a low P-value indicates statistical variation (heterogeneity) beyond chance.

The I^2 percentage will be interpreted as follows:

- 0% - 30% may not be important.
- 30% - 60% may represent moderate heterogeneity*
- 50% - 90% may represent substantial heterogeneity*
- 75% - 100% represents considerable heterogeneity*

[*the importance of the observed I^2 value depends on; magnitude and direction of effects and strength of evidence for heterogeneity such as P-value from X^2 or a Confidence Interval for I^2].

Generation of statistical heterogeneity can be a consequence of clinical (participants, interventions and outcomes) and/or methodological (study design and risk of bias) diversity or due to random error (chance) alone. T^2 represents the estimated standard deviation of underlying effects across studies. The exact model utilised for meta-analysis will be based upon the level of heterogeneity within our data; with a random effects model used if it is high and a fixed-effects analysis if moderate.

Data Synthesis and statistical analysis

Outcomes will be tabulated, with descriptive statistics performed as appropriate. Similarly, the detection rate of each modality will be compared and synthesised where possible. Synthesis will be performed utilising Review Manager (RevMan 5.2.6) and an assessment of heterogeneity will be made. Based upon this, meta-analysis will be carried out comparing Cook-Swartz Doppler to clinical monitoring; ideally utilising randomised controlled trials, but good quality observational studies will also be considered.

Rate of flap salvage will be compared between modalities of monitoring to establish any correlation. The false positive and negative rates of the Cook-Swartz Implantable Doppler will be calculated. If possible, the efficacy of the Cook-Swartz Implantable Doppler in different flap types and locations will be established.

Dissemination

The number of free flaps that are compromised per year mean that improvements need to be made to monitoring protocols. It is possible that the Cook-Swartz Doppler may well represent a useful tool for such improvement. As such, the authors hope to disseminate the findings as widely as possible, irrespective of results as they add to wider corpora of information. The systematic review will be published in a peer-reviewed journal and include a number of recommendations as its conclusion based upon the evidence contained within. Given the wide range of specialities now utilising flaps, it will be presented at a wide range of national and international conferences. Updates of the review could be conducted as more information becomes available to guide best practice and further maintain the quality of evidence.

Contributorship Statement

RAA - concept, intial drafting, critical revision, approval of manuscript to be submitted

BG - drafting, critical revision, approval of manuscript to be submitted

AJF - drafting, critical revision, approval of manuscript to be submitted

TWHB - concept, critical revision, approval of manuscript to be submitted

DO - concept, critical revision, approval of manuscript to be submitted

Funding: No funding was received for this systematic review

Conflicts of interest: The authors declare no potential conflicts of interest

Protocol Registration: PROSPERO – National Institute of Health Research (NIHR) Prospective Register of Systematic Reviews CRD42013005818

References:

1. Jallali N, Ridha H, Butler PE. Postoperative monitoring of free flaps in UK plastic surgery units. Microsurgery. 2005;25(6):469-72.
2. Schmulder A, Gur E, Zaretski A. Eight-year experience of the Cook-Swartz Doppler in free-flap operations: microsurgical and reexploration results with regard to a wide spectrum of surgeries. Microsurgery. 2011;31(1):1-6.
3. Liu Y, Zhao YF, Huang JT, Wu Y, Jiang L, Wang GD, et al. Analysis of 13 cases of venous compromise in 178 radial forearm free flaps for intraoral reconstruction. Int J Oral Maxillofac Surg. 2012;41(4):448-52.
4. Hidalgo DA, Jones CS. The role of emergent exploration in free-tissue transfer: a review of 150 consecutive cases. Plast Reconstr Surg. 1990;86(3):492-8; discussion 9-501.
5. Ali R, Bernier C, Lin YT, Ching WC, Rodriguez EP, Cardenas-Mejia A, et al. Surgical strategies to salvage the venous compromised deep inferior epigastric perforator flap. Ann Plast Surg. 2010;65(4):398-406.
6. Yu P, Chang DW, Miller MJ, Reece G, Robb GL. Analysis of 49 cases of flap compromise in 1310 free flaps for head and neck reconstruction. Head Neck. 2009;31(1):45-51.
7. Chen K-T, Mardini S, Wei F-C. Intraoperative Vascular Findings Predict Salvage Outcome in Free Flaps with Circulatory Compromise. J Reconstr Microsurg. 2006;22(07):A020.
8. Utley DS, Koch RJ, Goode RL. The failing flap in facial plastic and reconstructive surgery: role of the medicinal leech. Laryngoscope. 1998;108(8 Pt 1):1129-35.
9. Bibbo C, Fritsche T, Stemper M, Hall M. Flap infection associated with medicinal leeches in reconstructive surgery: two new drug-resistant organisms. J Reconstr Microsurg. 2013;29(7):457-60.
10. Dabb RW, Malone JM, Leverett LC. The use of medicinal leeches in the salvage of flaps with venous congestion. Ann Plast Surg. 1992;29(3):250-6.
11. Smit JM, Zeebregts CJ, Acosta R, Werker PM. Advancements in free flap monitoring in the last decade: a critical review. Plast Reconstr Surg. 2010;125(1):177-85.
12. Rozen WM, Enajat M, Whitaker IS, Lindkvist U, Audolfsson T, Acosta R. Postoperative monitoring of lower limb free flaps with the Cook-Swartz implantable Doppler probe: A clinical trial. Microsurgery. 2010;30(5):354-60.
13. Dragu A, Linke R, Kuwert T, Unglaub F, Kneser U, Stürzl M, et al. Tc-99m Sestamibi SPECT/CT as a New Tool for Monitoring Perfusion and Viability of Buried Perforator Based Free Flaps in Breast Reconstruction After Breast Cancer. Clin Nucl Med. 2010;35(1):36-7 10.1097/RLU.0b013e3181c614d.
14. Top H, Sarikaya A, Aygit AC, Benlier E, Kiyak M. Review of monitoring free muscle flap transfers in reconstructive surgery: role of 99mTc sestamibi scintigraphy. Nucl Med Commun. 2006;27(1):91-8.
15. Lin SJ, Nguyen MD, Chen C, Colakoglu S, Curtis MS, Tobias AM, et al. Tissue oximetry monitoring in microsurgical breast reconstruction decreases flap loss and improves rate of flap salvage. Plast Reconstr Surg. 2011;127(3):1080-5.
16. Jyranki J, Suominen S, Vuola J, Back L. Microdialysis in clinical practice: monitoring intraoral free flaps. Ann Plast Surg. 2006;56(4):387-93.

17. Smit JM, Whitaker IS, Liss AG, Audolfsson T, Kildal M, Acosta R. Post operative monitoring of microvascular breast reconstructions using the implantable Cook-Swartz doppler system: a study of 145 probes & technical discussion. J Plast Reconstr Aesthet Surg. 2009;62(10):1286-92.
18. Swartz WM, Jones NF, Cherup L, Klein A. Direct monitoring of microvascular anastomoses with the 20-MHz ultrasonic Doppler probe: an experimental and clinical study. Plast Reconstr Surg. 1988;81(2):149-61.
19. Rozen WM, Chubb D, Whitaker IS, Acosta R. The efficacy of postoperative monitoring: a single surgeon comparison of clinical monitoring and the implantable Doppler probe in 547 consecutive free flaps. Microsurgery. 2010;30(2):105-10.
20. Guillemaud JP, Seikaly H, Cote D, Allen H, Harris JR. The implantable Cook-Swartz Doppler probe for postoperative monitoring in head and neck free flap reconstruction. Arch Otolaryngol Head Neck Surg. 2008;134(7):729-34.
21. Paydar KZ, Hansen SL, Chang DS, Hoffman WY, Leon P. Implantable venous Doppler monitoring in head and neck free flap reconstruction increases the salvage rate. Plast Reconstr Surg. 2010;125(4):1129-34.
22. Kind GM, Buntic RF, Buncke GM, Cooper TM, Siko PP, Buncke HJ, Jr. The effect of an implantable Doppler probe on the salvage of microvascular tissue transplants. Plast Reconstr Surg. 1998;101(5):1268-73; discussion 74-5.
23. Pryor SG, Moore EJ, Kasperbauer JL. Implantable Doppler flow system: experience with 24 microvascular free-flap operations. Otolaryngol Head Neck Surg. 2006;135(5):714-8.
24. Poder TG, Fortier PH. Implantable Doppler in monitoring free flaps: a cost-effectiveness analysis based on a systematic review of the literature. Eur Ann Otorhinolaryngol Head Neck Dis. 2013;130(2):79-85.
25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
26. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009) [updated 01 July 201322 August 2013]. Available from: http://www.cebm.net/?o=1025.
27. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
28. Higgins. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011 [[Accessed: 20 June 2013]]. Available from: www.cochrane-handbook.org.
29. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002.

The efficacy of the Cook-Swartz implantable Doppler in the detection of free flap compromise: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004253.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Feb-2014
Complete List of Authors:	Agha, Riaz; Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK, Plastic Surgery department Gundogan, Buket; University College London Medical School, London,UK, Fowler, Alexander; Barts and the London School of medicine and dentistry, Bragg, Thomas; Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK, Plastic Surgery department Orgill, Dennis; Brigham and Women's Hospital, Boston,, Division of Plastic Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice, Surgery, Ear, nose and throat/otolaryngology
Keywords:	SURGERY, Plastic & reconstructive surgery < SURGERY, Otolaryngology < SURGERY, Head & neck surgery < SURGERY

SCHOLARONE™ Manuscripts

The efficacy of the Cook-Swartz implantable Doppler in the detection of free flap compromise: A systematic review protocol

REVIEW INFORMATION

Authors: Riaz A. Agha[a], Buket Gundogan[b], Alexander J. Fowler[c], Thomas WH Bragg[a], Dennis P. Orgill[d]

Contact person: Buket Gundogan (buket.gundogan.11@ucl.ac.uk)

Institutions: a – Department of Plastic Surgery, Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK

b – University College London Medical School, London, UK

c – Barts and the London School of Medicine and Dentistry, QMUL, London, UK

d – Division of Plastic Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA

ABSTRACT

Introduction

The Cook-Swartz implantable Doppler monitors venous or arterial blood flow from free flaps and can detectfree flap compromise. Previous studies have shown that the use of this Doppler can improve detection and salvage rates as it provides an earlier warning than the current method of clinical assessment. Such studies assert that the implantable Doppler is of great value in monitoring of free flaps in current microsurgical units. This systematic review aims to compare the efficacy of the Cook-Swartz implantable Doppler in monitoring free flap compromise against conventional clinical free flap monitoring techniques.

Methods and analysis

Various electronic databases will be systematically searched for studies which compare the use of Cook-Swartz implantable Doppler with clinical assessment. The selected studies will then have their titles and abstracts screened by two authors. Articles selected after title and abstract screen will have full text downloaded and the complete article will be assessed for suitability. Once articles have been selected for inclusion, data extraction will take place. For the data analysis, the outcomes of the studies will be tabulated, with descriptive statistics performed as appropriate and the detection rate of the Doppler and clinical assessment will be compared and synthesised where possible.

Ethics and Dissemination

The authors hope to disseminate the findings as widely as possible. This systematic review will be published in a peer-reviewed journal and include a number of recommendations as its conclusion based upon the evidence contained within. Given the wide range of specialities now utilising flaps, it will be presented at a wide range of national and international conferences.

Protocol Registration in PROSPERO: CRD42013005818

By 28th January 2014, the literature search and data extraction had been ongoing for some time. These steps were revised in line with peer review comments.

BACKGROUND

Free flap reconstruction

Free flap reconstruction for large tissue defects is increasingly common and plays an important role in the field of plastic and reconstructive surgery.[1] Such surgery necessitates a microsurgical anastamosis from the harvested flap to the recipient using minute sutures. Data suggests that the commonest cause of failure is a problem with the venous anastamosis occurring within the first 24 to 48 hours postoperatively.[2,3, 4] This problem affects up to 20% of all free flap reconstructions, depending upon their location and entails significant physical, psychological and emotional morbidity for patients.[5, 6 7]

Flap failure often necessitates further general anaesthetics and operations. Due to the time critical nature of flap failure, reoperation may occur out of hours, which provides further logistical and practical challenges.[7] Initially, an attempt is made to salvage the flap, if this fails, then the flap is removed and an alternative reconstructive approach may be required. In some cases, venous congestion may require blood drainage; for example by use of medicinal leeches,[8] which is potentially highly unpleasant for patients and predisposes them to infection and anaemia.[9] Patients therefore require careful wound inspection, surveillance of haemoglobin and prophylactic antibiotics to protect them from further complications.[8, 10]

Monitoring of free flaps

Early recognition of flap compromise is the primary aim of every microsurgical unit. Prompt intervention and rescue is critical for ensuring flap survival. However, the complexities of free flap microcirculation are often difficult to assess, and there are a wide array of possible monitoring modalities.[11] The commonest method of monitoring is carried out clinically and is based upon subjective clinical observations. These tests are carried out on an island of skin or 'skin paddle' – an area of skin considered to be indicative of the whole flap's arterial perfusion and venous drainage.[12] Such tests may include the colour, capillary refill or blanching time, skin temperature, turgor, and degree of bleeding in response to pin-prink and use of a handheld doppler device.[13]

Unlike solid organ transplantation, there is no objective assessment - such as decreased urine output in renal transplantation. Similarly, there are currently no suitable imaging modalities for assessing microvascular flow and specifically slow venous flow problems, though there are reports in the literature of the use of nuclear medicine techniques in successful monitoring.[14] A number of small studies have highlighted the use of Single-Positron Emission Computed Tomography (SPECT) in the determination of free flap compromise.[15] However, large comparative studies are required with standardised techniques to further define the role of this modality in the assessment of free flap compromise. Early compromise, which entails the large majority of flap failure, is often asymptomatic. Pain, bleeding and skin changes can take a while to develop, potentially increasing ischaemic times and reducing the possibility of successful salvage.[16]

Some free flaps are very challenging to monitor adequately, such as vascularised bone and muscle flaps; especially those that have been covered with a skin graft and cutaneous flaps in non-Caucasian skin. Some flaps, such as buried flaps within the head and neck are impossible to monitor by visual, clinical assessment and in such circumstances, attempts have been made to enhance clinical monitoring using microdialysis.[11, 17] However, this can take up to 30 minutes to get a reading, necessitates training to learn a technique and analyse results, does not directly measure flow and costs almost $52,000 per monitor plus additional costs of up to $570 per flap.[11]

The Cook-Swartz Implantable Doppler

The Cook-Swartz implantable Doppler monitors the venous flow from free flaps and obtained its CE mark in 2006.[18] Since then it has been distributed widely in both Europe and the rest of the world.[18] It is the only device currently on the market that allows this monitoring and is protected by patent. It consists of a 20 MHz ultrasonic Doppler crystal, a silicone cuff and a monitor unit.[19, 20] This cuff secures the Doppler to the flap's vein at the time of the operation and is placed downstream of the microvascular anastamosis.[20] The Doppler provides monitoring for 5-10 days postoperatively and is removed by simple traction.[18] A number of studies have shown that use of this device increases success and salvage rates as it provides an earlier warning that the current method of clinical monitoring.[12, 21, 22]

The potential of the Cook-Swartz Doppler

The use of the Cook-Swartz Doppler in the assessment of such flaps has demonstrated improved detection times.[2, 12, 22, 23] This technology is needed now more than ever as the indications for, and therefore absolute number of, free flaps have increased. Indications for flaps include following resection of breast tumours, head and neck cancers, skin cancers, major burns and infections. Often these may be 'cross-speciality' flaps, for example with orthopaedics to cover exposed metal work in lower limb fractures. Changes to working practices mean that these patients may be returned to an orthopaedic or general surgical ward where monitoring is performed by non-specialist nurses who may not be used to monitoring flaps, let alone over night and in challenging settings such as low light.

Why is a systematic review of this required?

To our knowledge, there has only been one systematic review involving the Cook-Swartz Implantable Doppler. Poder and Fortier investigated the efficacy and cost effectiveness of the implantable Doppler.[24] However, we aim to investigate and further clarify the role of the Doppler as a monitoring technique by comparing it to clinical assessment. Clinical assessment is the most widely used technique and as such the standard against which the Doppler should be compared. Further clarifying the role and possible benefit of the Cook-Swartz Doppler in the detection of free flap compromise would allow modification of practice and guidelines in line with the best evidence. We realise that previous reviews were limited by the quality of evidence available, but a number of studies have been published since the last review and therefore an updated review is required.

OBJECTIVES

Our objective is to perform a comprehensive systematic review of the implantable Doppler in the detection of free flap compromise.

Primary objective:

To compare the efficacy of the Cook-Swartz implantable Doppler versus clinical assessment in the detection of free flap compromise and flap salvage.

Secondary objectives:

To determine the absolute indications for use of the Doppler (if any). Quanitfy the sensitivity, specificity, positive and negative predictive values of the Doppler. To describe complications associated with Doppler use.

METHODS

This systematic review will be conducted according to the recommendations outlined in the Cochrane Handbook for reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25]

Criteria for selecting studies:

The following search criteria were specifically devised to locate studies specifically pertaining to the use of the Cook-Swartz Doppler and to provide evidence for the objectives previously stated.

Types of studies

Any study comparing the use of Cook-Swartz implantable doppler with clinical assessment in detecting the failure of free flaps will be included. Articles must describe use of the implantable doppler specifically and may be of any grade of evidence (1 to 5 as defined by the Oxford Centre for Evidence-Based Medicine).[26]

Any article where data is duplicated will be excluded, as will articles not describing original data; such as editorials, letters regarding other articles and discussion pieces. Unpublished reports will be included if the methodology and results are accessible in written form.

Types of participants

Human subjects of any age who have undergone free flap surgery. There will be no limitation on location of the flap or technique utilised.

Types of interventions

Any article describing use of the Cook-Swartz Doppler in the detection of free flap compromise would be considered, and articles won't be excluded based on type of flap. Articles will only be considered if they include a group monitored by clinical detection for comparison with the Cook-Swartz Doppler.

Types of comparator

Cook-Swartz implantable Doppler used on the venous or arterial pedicle of a free flap attached by any means and used to monitor free flaps post-operatively. Clinical assessment of free flaps including, but not limited to; skin colour, turgor, surface temperature, capillary refill time or handheld Doppler.

Types of outcome measures

Primary outcome:

Flap failure rate, defined as the number of free flaps lost divided by the total number of flaps This outcome will be calculated for both doppler and clinically monitored flaps.

Secondary outcomes:

Sensitivity, specificity, positive predictive value and negative predictive value.

Time to detection will be reported where possible and compared between clinically monitored and Doppler monitored flaps.

Any complications associated with flap use will be described

Search methods for identification of studies

Electronic Searches

The following electronic databases will be searched to 24th September 2013: MEDLINE, EMBASE, PsycINFO, Ebosco, Cochrane Database of Systematic Reviews, CINAHL, SCOPUS, SciELO, NHS evidence, www.uptodate.com, http://clinicaltrials.gov/, http://www.who.int/ictrp/en/, http://www.controlled-trials.com/

Search terms and keywords

The search strategy has been developed to locate papers related specifically to the Cook-Swartz implantable Doppler. This search will utilise the English language keywords combined with Boolean logical operators. Therefore the following terms will be utilised: "*Implantable doppler*" OR "*Cook-Swartz implantable doppler*" OR "*Cook-Swartz Implantable doppler*".

The search will not be limited by language. Any non-English articles identified will proceed to title and abstract screening and the full text obtained if required. If full text is not available, then the authors will be contacted to obtain an English language copy of the full text. Failing this, colleagues speaking the language will be contacted to translate. Google Translate will be utilised as a last resort.

Other resources

A hand search of the references of articles located by the search strategy will be used to identify any relevant citations within the grey literature. Active researchers will be contacted to identify any other published or unpublished work. An active researcher is defined as one who has published more than three articles in the field in the last five years, or one in the last two.

Identification and Selection of articles

Studies identified by the electronic and manual search strategy will be listed. Results including citation, title and abstracts will be populated into EndNote® (Thomson Reuters, New York, NY, USA) and duplicates removed. Titles and abstracts will be screened by two authors (BG and AJF), any conflicts not resolvable between the two will be referred to the lead author (RA) for resolution. Articles selected after title and abstract screen will have full text downloaded and a further assessment made. Once articles have been selected for inclusion, data extraction will take place.

Data extraction and management

Data will be extracted independently by two authors (BG and AJF) utilising a standard extraction form where all data for each study will be collated (Appendix A). Any conflict of extraction will be resolved by discussion; where resolution this isn't possible, the lead author (RA) will make a final decision. This data will then be entered into a Microsoft Excel ® 2011 database (Microsoft, Redmond, WA, USA). Data collected will constitute three main areas:

1) **Article information**
   - Title
   - Authors
   - Year of publication
   - Journal
2) **Characteristics**
   - Setting and Location of the study
   - Number of patients
   - Range of patient age
   - Flap types included
   - Clinical method of assessment
   - Doppler method of assessment (Arterial vs. Venous)
3) **Results (divided clinical and doppler)**
   - Number of patients per group
   - Specific flaps in groups (where applicable)
   - Detected

- Flap Salvage
- Needless theatre return
- Complications
- Lost flaps without any signs
- Flaps correctly monitored

Assessment of study quality and bias in included studies

Quality of evidence can be assessed based upon a number of criteria; we will be specifically utilising the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system as proposed by Balshem et al.[27] This will allow us to determine the quality of the evidence that is being utilised in the data analysis of this topic.

If we locate any Randomised Controlled Trials (RCTs) we will utilise the Cochrane risk of bias tool and compare outcomes to published trial protocols. Any information missing from studies will be documented and assessed to ascertain the risk of incomplete statistical sets.

Assessment of publication bias

To ascertain if studies with negative outcomes are not being published ("publication bias"), we will visually assess funnel plot asymmetry.[28, 29] Where both positive and negative results are published, the plot should resemble a symmetrical, inverted funnel. The prevision of the estimated intervention effect will increase as the size of the sample included in the study increases. Smaller studies will therefore scatter widely at the bottom, with larger, more powerful studies grouping more narrowly at the top. The asymmetrical distribution of standard error on analysis of the funnel plot would indicate publication bias.

Assessment of Heterogeneity

Heterogeneity between studies will be assessed using Higgins and Thompson's I^2, which measures the percentage variability in result attributable to heterogeneity between studies rather than sampling error[28]. Variability in the intervention effects in studies will be tested for statistical heterogeneity utilising Tau-squared (T^2), I^2 and chi-squared (X^2) with corresponding P-values calculated; the Cochrane tests.

The value of X^2 statistics in the forest plot presents the assessment of whether the differences in results are compatible with chance alone. A large value of X^2 test relative to its degree of freedom (df) or a low P-value indicates statistical variation (heterogeneity) beyond chance.

The I^2 percentage will be interpreted as follows:

- 0% - 30% may not be important.
- 30% - 60% may represent moderate heterogeneity*
- 50% - 90% may represent substantial heterogeneity*
- 75% - 100% represents considerable heterogeneity*

[*the importance of the observed I^2 value depends on; magnitude and direction of effects and strength of evidence for heterogeneity such as P-value from X^2 or a Confidence Interval for I^2].[28]

Generation of statistical heterogeneity can be a consequence of clinical (participants, interventions and outcomes) and/or methodological (study design and risk of bias) diversity or due to random error (chance) alone. T^2 represents the estimated standard deviation of underlying effects across studies. The exact model utilised for meta-analysis will be based upon the level of heterogeneity within our data; with a random effects model used if it is high and a fixed-effects analysis if moderate.

Data Synthesis and statistical analysis

Outcomes will be tabulated, with descriptive statistics performed as appropriate. Similarly, the detection rate of each modality will be compared and synthesised where possible. Synthesis will be performed utilising Review Manager (RevMan 5.2.6) and an assessment of heterogeneity will be made. Based upon this, meta-analysis will be carried out comparing Cook-Swartz Doppler to clinical monitoring; ideally utilising randomised controlled trials, but good quality observational studies will also be considered.

Rate of flap salvage will be compared between modalities of monitoring to establish any correlation. The false positive and negative rates of the Cook-Swartz Implantable Doppler will be calculated. If possible, the efficacy of the Cook-Swartz Implantable Doppler in different flap types and locations will be established.

Sub Group Analysis

Subgroup analyses will be undertaken of the following groups where available:

- Different flap type (if >3 studies describing specific flap types)
- Venous vs. Arterial Doppler probe placement

- Different anatomic locations (if >3 studies describe the same anatomic locations)

Dissemination

The number of free flaps that are compromised per year mean that improvements need to be made to monitoring protocols. It is possible that the Cook-Swartz Doppler may well represent a useful tool for such improvement. As such, the authors hope to disseminate the findings as widely as possible, irrespective of results as they add to wider corpora of information. The systematic review will be published in a peer-reviewed journal and include a number of recommendations as its conclusion based upon the evidence contained within. Given the wide range of specialities now utilising flaps, it will be presented at a wide range of national and international conferences. Updates of the review could be conducted as more information becomes available to guide best practice and further maintain the quality of evidence.

Funding: No funding was received for this systematic review

Contributorsip Statement:

RAA - concept, intial drafting, critical revision, approval of manuscript to be submitted

BG - drafting, critical revision, approval of manuscript to be submitted

AJF - drafting, critical revision, approval of manuscript to be submitted

TWHB - concept, critical revision, approval of manuscript to be submitted

DO - concept, critical revision, approval of manuscript to be submitted

Conflicts of interest: The authors declare no potential conflicts of interest

Protocol Registration: PROSPERO – National Institute of Health Research (NIHR) Prospective Register of Systematic Reviews CRD42013005818

References:

1. Wong AK, Joanna Nguyen T, Peric M, et al. Analysis of risk factors associated with microvascular free flap failure using a multi-institutional database. Microsurgery. 2014.
2. Schmulder A, Gur E, Zaretski A. Eight-year experience of the Cook-Swartz Doppler in free-flap operations: microsurgical and reexploration results with regard to a wide spectrum of surgeries. Microsurgery. 2011;31(1):1-6.
3. Liu Y, Zhao YF, Huang JT, et al. Analysis of 13 cases of venous compromise in 178 radial forearm free flaps for intraoral reconstruction. Int J Oral Maxillofac Surg. 2012;41(4):448-52.
4. Hidalgo DA, Jones CS. The role of emergent exploration in free-tissue transfer: a review of 150 consecutive cases. Plast Reconstr Surg. 1990;86(3):492-8; discussion 9-501.
5. Ali R, Bernier C, Lin YT, et al. Surgical strategies to salvage the venous compromised deep inferior epigastric perforator flap. Ann Plast Surg. 2010;65(4):398-406.
6. Yu P, Chang DW, Miller MJ, et al. Analysis of 49 cases of flap compromise in 1310 free flaps for head and neck reconstruction. Head Neck. 2009;31(1):45-51.
7. Chen K-T, Mardini S, Wei F-C. Intraoperative Vascular Findings Predict Salvage Outcome in Free Flaps with Circulatory Compromise. J Reconstr Microsurg. 2006;22(07):A020.
8. Utley DS, Koch RJ, Goode RL. The failing flap in facial plastic and reconstructive surgery: role of the medicinal leech. Laryngoscope. 1998;108(8 Pt 1):1129-35.
9. Bibbo C, Fritsche T, Stemper M, et al. Flap infection associated with medicinal leeches in reconstructive surgery: two new drug-resistant organisms. J Reconstr Microsurg. 2013;29(7):457-60.
10. Dabb RW, Malone JM, Leverett LC. The use of medicinal leeches in the salvage of flaps with venous congestion. Ann Plast Surg. 1992;29(3):250-6.
11. Smit JM, Zeebregts CJ, Acosta R, et al. Advancements in free flap monitoring in the last decade: a critical review. Plast Reconstr Surg. 2010;125(1):177-85.
12. Rozen WM, Enajat M, Whitaker IS, et al. Postoperative monitoring of lower limb free flaps with the Cook-Swartz implantable Doppler probe: A clinical trial. Microsurgery. 2010;30(5):354-60.
13. Jallali N, Ridha H, Butler PE. Postoperative monitoring of free flaps in UK plastic surgery units. Microsurgery. 2005;25(6):469-72.
14. Dragu A, Linke R, Kuwert T, et al. Tc-99m Sestamibi SPECT/CT as a New Tool for Monitoring Perfusion and Viability of Buried Perforator Based Free Flaps in Breast Reconstruction After Breast Cancer. Clin Nucl Med. 2010;35(1):36-7 10.1097/RLU.0b013e3181c614d.
15. Top H, Sarikaya A, Aygit AC, et al. Review of monitoring free muscle flap transfers in reconstructive surgery: role of 99mTc sestamibi scintigraphy. Nucl Med Commun. 2006;27(1):91-8.
16. Lin SJ, Nguyen MD, Chen C, et al. Tissue oximetry monitoring in microsurgical breast reconstruction decreases flap loss and improves rate of flap salvage. Plast Reconstr Surg. 2011;127(3):1080-5.

17. Jyranki J, Suominen S, Vuola J, et al. Microdialysis in clinical practice: monitoring intraoral free flaps. Ann Plast Surg. 2006;56(4):387-93.
18. Smit JM, Whitaker IS, Liss AG, et al. Post operative monitoring of microvascular breast reconstructions using the implantable Cook-Swartz doppler system: a study of 145 probes & technical discussion. J Plast Reconstr Aesthet Surg. 2009;62(10):1286-92.
19. Swartz WM, Jones NF, Cherup L, et al. Direct monitoring of microvascular anastomoses with the 20-MHz ultrasonic Doppler probe: an experimental and clinical study. Plast Reconstr Surg. 1988;81(2):149-61.
20. Rozen WM, Chubb D, Whitaker IS, et al. The efficacy of postoperative monitoring: a single surgeon comparison of clinical monitoring and the implantable Doppler probe in 547 consecutive free flaps. Microsurgery. 2010;30(2):105-10.
21. Paydar KZ, Hansen SL, Chang DS, et al. Implantable venous Doppler monitoring in head and neck free flap reconstruction increases the salvage rate. Plast Reconstr Surg. 2010;125(4):1129-34.
22. Kind GM, Buntic RF, et al. The effect of an implantable Doppler probe on the salvage of microvascular tissue transplants. Plast Reconstr Surg. 1998;101(5):1268-73; discussion 74-5.
23. Pryor SG, Moore EJ, Kasperbauer JL. Implantable Doppler flow system: experience with 24 microvascular free-flap operations. Otolaryngol Head Neck Surg. 2006;135(5):714-8.
24. Poder TG, Fortier PH. Implantable Doppler in monitoring free flaps: a cost-effectiveness analysis based on a systematic review of the literature. Eur Ann Otorhinolaryngol Head Neck Dis. 2013;130(2):79-85.
25. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
26. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009) [updated 01 July 201322 August 2013]. Available from: http://www.cebm.net/?o=1025.
27. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
28. Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011. Available from: www.cochrane-handbook.org.
29. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002.

The efficacy of the Cook-Swartz implantable Doppler in the detection of free flap compromise: A systematic review protocol

REVIEW INFORMATION

Authors: Riaz A. Agha[a], Buket Gundogan[b], Alexander J. Fowler[c], Thomas WH Bragg[a], Dennis P. Orgill[d]

Contact person: Buket Gundogan (buket.gundogan.11@ucl.ac.uk)

Institutions: a – Department of Plastic Surgery, Stoke Mandeville Hospital, Mandeville Road, Ayelsbury, Bucks, HP21 8AL, UK

b – University College London Medical School, London, UK

c – Barts and the London School of Medicine and Dentistry, QMUL, London, UK

d – Division of Plastic Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA

Funding: No funding was received for this systematic review

Conflicts of interest: The authors declare no potential conflicts of interest

Protocol Registration: PROSPERO – National Institute of Health Research (NIHR) Prospective Register of Systematic Reviews CRD42013005818

ABSTRACT

Introduction

The Cook-Swartz implantable Doppler monitors venous or arterial blood flow from free flaps and can detectfree flap compromise. Previous studies have shown that the use of this Doppler can improve detection and salvage rates as it provides an earlier warning than the current method of clinical assessment. Such studies assert that the implantable Doppler is of great value in monitoring of free flaps in current microsurgical units. This systematic review aims to compare the efficacy of the Cook-Swartz implantable Doppler in monitoring free flap compromise against conventional clinical free flap monitoring techniques.

Methods and analysis

Various electronic databases will be systematically searched for studies which compare the use of Cook-Swartz implantable Doppler with clinical assessment. The selected studies will then have their titles and abstracts screened by two authors. Articles selected after title and abstract screen will have full text downloaded and the complete article will be assessed for suitability. Once articles have been selected for inclusion, data extraction will take place. For the data analysis, the outcomes of the studies will be tabulated, with descriptive statistics performed as appropriate and the detection rate of the Doppler and clinical assessment will be compared and synthesised where possible.

Ethics and Dissemination

The authors hope to disseminate the findings as widely as possible. This systematic review will be published in a peer-reviewed journal and include a number of recommendations as its conclusion based upon the evidence contained within. Given the wide range of specialities now utilising flaps, it will be presented at a wide range of national and international conferences.

Protocol Registration in PROSPERO: CRD42013005818

By 28th January 2014, the literature search and data extraction had been ongoing for some_time. These steps were revised in line with peer review comments.

BACKGROUND

Free flap reconstruction

Free flap reconstruction for large tissue defects is increasingly common and plays an important role in the field of plastic and reconstructive surgery.[1] Such surgery necessitates a microsurgical anastamosis from the harvested flap to the recipient using minute sutures. Data suggests that the commonest cause of failure is a problem with the venous anastamosis occurring within the first 24 to 48 hours postoperatively.[2,3, 4] This problem affects up to 20% of all free flap reconstructions, depending upon their location and entails significant physical, psychological and emotional morbidity for patients.[5, 6 7]

Flap failure often necessitates further general anaesthetics and operations. Due to the time critical nature of flap failure, reoperation may occur out of hours, which provides further logistical and practical challenges.[7] Initially, an attempt is made to salvage the flap, if this fails, then the flap is removed and an alternative reconstructive approach may be required. In some cases, venous congestion may require blood drainage; for example by use of medicinal leeches,~~.~~[8] which ~~This~~ is potentially highly unpleasant for patients and predisposes them to infection and anaemia.[9] Patients therefore require careful wound inspection, surveillance of haemoglobin and prophylactic antibiotics to protect them from further complications.[8, 10]

Monitoring of free flaps

Early recognition of flap compromise is the primary aim of every microsurgical unit. Prompt intervention and rescue is critical for ensuring flap survival. However, the complexities of free flap microcirculation are often difficult to assess, and there are a wide array of possible monitoring modalities.[11] ~~At present, m~~The commonest method of monitoring is carried out clinically and is based upon subjective clinical observations. These tests are carried out on an island of skin or ‘skin paddle’ – an area of skin considered to be indicative of the whole flap's arterial perfusion and venous drainage.[12] Such tests may include the colour, capillary refill or blanching time, skin temperature, turgor, and degree of bleeding in response to pin-prink and use of a handheld doppler device.[13]

Unlike solid organ transplantation, there is no objective assessment - such as decreased urine output in renal transplantation. Similarly, there are currently no suitable imaging modalities for assessing microvascular flow and specifically slow venous flow problems, though there are reports in the literature of the use of nuclear medicine techniques in successful monitoring.[14] A number of small studies have highlighted the use of Single-Positron Emission Computed Tomography (SPECT) in the determination of free flap compromise.[15] However, large comparative studies are required with standardised techniques to further define the role of this modality in the assessment of free flap compromise. Early compromise, which entails the large majority of flap failure, is often asymptomatic. Pain, bleeding and skin changes can take a while to develop, potentially increasing ischaemic times and reducing the possibility of successful salvage.[16]

Some free flaps are very challenging to monitor adequately, such as vascularised bone and muscle flaps; especially those that have been covered with a skin graft and cutaneous flaps in non-Caucasian skin. Some flaps, such as buried flaps within the head and neck are impossible to monitor by visual, clinical assessment and in such circumstances, attempts have been made to enhance clinical monitoring using microdialysis.[11, 17] However, this can take up to 30 minutes to get a reading, necessitates training to learn a technique and analyse results, does not directly measure flow and costs almost $52,000 per monitor plus additional costs of up to $570 per flap.[11]

The Cook-Swartz Implantable Doppler

The Cook-Swartz implantable Doppler monitors the venous flow from free flaps and obtained its CE mark in 2006.[18] Since then it has been distributed widely in both Europe and the rest of the world.[18] It is the only device currently on the market that allows this monitoring and is protected by patent. It consists of a 20 MHz ultrasonic Doppler crystal, a silicone cuff and a monitor unit.[19, 20] This cuff secures the Doppler to the flap's vein at the time of the operation and is placed downstream of the microvascular anastamosis.[20] The Doppler provides monitoring for 5-10 days postoperatively and is removed by simple traction.[18] A number of studies have shown that use of this device increases success and salvage rates as it provides an earlier warning that the current method of clinical monitoring.[12, 21, 22]

The potential of the Cook-Swartz Doppler

The use of the Cook-Swartz Doppler in the assessment of such flaps has demonstrated improved detection times.[2, 12, 22, 23] This technology is needed now more than ever as the indications for, and therefore absolute number of, free flaps have increased. Indications for flaps include following resection of breast tumours, head and neck cancers, skin cancers, major burns and infections. Often these may be 'cross-speciality' flaps, for example with orthopaedics to cover exposed metal work in lower limb fractures. Changes to working practices mean that these patients may be returned to an orthopaedic or general surgical ward where monitoring is performed by non-specialist nurses who may not be used to monitoring flaps, let alone over night and in challenging settings such as low light.

Why is a systematic review of this required?

To our knowledge, there has only been one systematic review involving the Cook-Swartz Implantable Doppler. Poder and Fortier investigated the efficacy and cost effectiveness of the implantable Doppler.[24] However, we aim to investigate and further clarify the role of the Doppler as a monitoring technique by comparing it to clinical assessment. Clinical assessment is the most widely used technique and as such the standard against which the Doppler should be compared. Further clarifying the role and possible benefit of the Cook-Swartz Doppler in the detection of free flap compromise would allow modification of practice and guidelines in line with the best evidence. We realise that previous reviews were limited by the quality of evidence available, but a number of studies have been published since the last review and therefore an updated review is required.

OBJECTIVES

Our objective is to perform a comprehensive systematic review of the implantable Doppler in the detection of free flap compromise.

Primary objective:

To compare the efficacy of the Cook-Swartz implantable Doppler versus clinical assessment in the detection of free flap compromise and flap salvage.

Secondary objectives:

To determine the absolute indications for use of the Doppler (if any). Quanitfy the sensitivity, specificity, ~~false positive and negative rates, salvage rates and number of associated complications.~~positive and negative predictive values of the Doppler. To describe complications associated with Doppler use.

METHODS

This systematic review will be conducted according to the recommendations outlined in the Cochrane Handbook for reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25]

Criteria for selecting studies:

The following search criteria were specifically devised to locate studies specifically pertaining to the use of the Cook-Swartz Doppler and to provide evidence for the objectives previously stated.

Types of studies

Any study comparing the use of Cook-Swartz implantable doppler with clinical assessment in detecting the failure of free flaps will be included. Articles must describe use of the implantable doppler specifically and may be of any grade of evidence (1 to 5 as defined by the Oxford Centre for Evidence-Based Medicine).[26]

Any article where data is duplicated will be excluded, as will articles not describing original data; such as editorials, letters regarding other articles and discussion pieces. Unpublished reports will be included if the methodology and results are accessible in written form.

Types of participants

Human subjects of any age who have undergone free flap surgery. There will be no limitation on location of the flap or technique utilised.

Types of interventions

Any article describing use of the Cook-Swartz Doppler in the detection of free flap compromise would be considered, and articles won't be excluded based on type of flap. ~~Ideally, t~~Articles will only be considered if they include a group monitored by clinical detection for comparison with the Cook-Swartz Doppler.~~his would be considered against a control group of clinical monitoring.~~

Types of comparator

Cook-Swartz implantable Doppler used on the venous or arterial pedicle of a free flap attached by any means and used to monitor free flaps post-operatively. Clinical assessment of free flaps including, but not limited to; skin colour, turgor, surface temperature, capillary refill time or handheld Doppler.

Types of outcome measures

Primary outcome:

Flap failure rate, defined as the number of free flaps lost divided by the total number of flapsThe rate of detection will be determined as the number of Doppler monitored flaps correctly identified as compromised divided by the total number of Doppler monitored flaps. This outcome will be compared calculated for both doppler andwith clinically monitored flapsing.

Secondary outcomes:

Sensitivity, specificity, positive predictive value and negative predictive value. The salvage rate will be the number of compromised flaps successfully salvaged divided by the total number of compromised flaps. The false positive rate is the number of flaps monitored by Doppler returned to theatre incorrectly divided by the total number of Doppler monitored flaps.

The false negative rate will be the number of flaps lost without any change in Doppler monitoring, divided by the total number of Doppler monitored flaps.

The true negative rates will be the number of flaps monitored without any change in Doppler and without any compromise divided by the total number of Doppler monitored flaps.

The rates for clinical assessment will be calculated as above and compared to that of the Doppler. Time to detection will be reported where possible and compared between clinically monitored and Doppler monitored flaps.

Any complications associated with flap use will be described

Search methods for identification of studies

Electronic Searches

The following electronic databases will be searched to 24th September 2013: MEDLINE, EMBASE, PsycINFO, Ebosco, Cochrane Database of Systematic Reviews, CINAHL, SCOPUS, SciELO, NHS evidence, www.uptodate.com, http://clinicaltrials.gov/, http://www.who.int/ictrp/en/, http://www.controlled-trials.com/

Search terms and keywords

The search strategy has been developed to locate papers related specifically to the Cook-Swartz implantable Doppler. This search will utilise the English language keywords combined with Boolean logical operators. Therefore the following terms will be utilised: "*Implantable doppler*" OR *"Cook-Swartz implantable doppler"* OR "*Cook-Swartz Implantable doppler*".

The search will not be limited by language. Any non-English articles identified will proceed to title and abstract screening and the full text obtained if required. If full text is not available, then the authors will be contacted to obtain an English language copy of the full text. Failing this, colleagues speaking the language will be contacted to translate. Google Translate will be utilised as a last resort.

Other resources

A hand search of the references of articles located by the search strategy will be used to identify any relevant citations within the grey literature. Active researchers will be contacted to identify any other published or unpublished work. An active researcher is defined as one who has published more than three articles in the field in the last five years, or one in the last two.

Identification and Selection of articles

Studies identified by the electronic and manual search strategy will be listed. Results including citation, title and abstracts will be populated into EndNote® (Thomson Reuters, New York, NY, USA) and duplicates removed. Titles and abstracts will be screened by two authors (BG and AJF), any conflicts not resolvable between the two will be referred to the lead author (RA) for resolution. Articles selected after title and abstract screen will have full text downloaded and a further assessment made. Once articles have been selected for inclusion, data extraction will take place.

Data extraction and management

Data will be extracted independently by two authors (BG and AJF) utilising a standard extraction form where all data for each study will be collated (Appendix A). Any conflict of extraction will be resolved by discussion; where resolution this isn't possible, the lead author (RA) will ~~have final say~~make a final decision. This data will then be entered into a Microsoft Excel ® 2011 database (Microsoft, Redmond, WA, USA). Data collected will constitute three main areas:

1) **Article information**
   - Title
   - Authors
   - Year of publication
   - Journal
2) **Characteristics**

- Setting and Location of the study
- Number of patients
- Range of patient age
- Flap types included
- Clinical method of assessment
- Doppler method of assessment (Arterial vs. Venous)

3) Results (divided clinical and doppler)

- Number of patients per group
- Specific flaps in groups (where applicable)
- Detected
- Flap Salvage
- Needless theatre return
- Complications
- Lost flaps without any signs
- Flaps correctly monitored

Assessment of study quality and bias in included studies

~~The quality of evidence included in this analysis needs to be established.~~ Quality of evidence can be assessed based upon a number of criteria; we will be specifically utilising the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system as proposed by Balshem et al.[27] This will allow us to determine the quality of the evidence that is being utilised in the data analysis of this topic.

If we locate any Randomised Controlled Trials (RCTs) we will utilise the Cochrane risk of bias tool and compare outcomes to published trial protocols. Any information missing from studies will be documented and assessed to ascertain the risk of incomplete statistical sets.

Assessment of publication bias

To ascertain if studies with negative outcomes are not being published ("publication bias"), we will visually assess funnel plot asymmetry.[28, 29] Where both positive and negative results are published, the plot should resemble a symmetrical, inverted funnel. The prevision of the estimated intervention effect will increase as the size of the sample included in the study increases. Smaller studies will therefore scatter widely at the bottom, with larger, more powerful studies grouping more narrowly at the top. The asymmetrical distribution of standard error on analysis of the funnel plot would indicate publication bias.

Assessment of Heterogeneity

Heterogeneity between studies will be assessed using Higgins and Thompson's I^2, which measures the percentage variability in result attributable to heterogeneity between studies rather than sampling error[28]. Variability in the intervention effects in studies will be tested for statistical heterogeneity utilising Tau-squared (T^2), I^2 and chi-squared (X^2) with corresponding P-values calculated; the Cochrane tests.

The value of X^2 statistics in the forest plot presents the assessment of whether the differences in results are compatible with chance alone. A large value of X^2 test relative to its degree of freedom (df) or a low P-value indicates statistical variation (heterogeneity) beyond chance.

The I^2 percentage will be interpreted as follows:

- 0% - 30% may not be important.
- 30% - 60% may represent moderate heterogeneity*
- 50% - 90% may represent substantial heterogeneity*
- 75% - 100% represents considerable heterogeneity*

[*the importance of the observed I^2 value depends on; magnitude and direction of effects and strength of evidence for heterogeneity such as P-value from X^2 or a Confidence Interval for I^2].[28]

Generation of statistical heterogeneity can be a consequence of clinical (participants, interventions and outcomes) and/or methodological (study design and risk of bias) diversity or due to random error (chance) alone. T^2 represents the estimated standard deviation of underlying effects across studies. The exact model utilised for meta-analysis will be based upon the level of heterogeneity within our data; with a random effects model used if it is high and a fixed-effects analysis if moderate.

Data Synthesis and statistical analysis

Outcomes will be tabulated, with descriptive statistics performed as appropriate. Similarly, the detection rate of each modality will be compared and synthesised where possible. Synthesis will be performed utilising Review Manager (RevMan 5.2.6) and an assessment of heterogeneity will be made. Based upon this, meta-analysis will be carried out comparing Cook-Swartz Doppler to clinical monitoring; ideally utilising randomised controlled trials, but good quality observational studies will also be considered.

Rate of flap salvage will be compared between modalities of monitoring to establish any correlation. The false positive and negative rates of the Cook-Swartz Implantable Doppler will be calculated. If possible, the efficacy of the Cook-Swartz Implantable Doppler in different flap types and locations will be established.

Sub Group Analysis

Subgroup analyses will be undertaken of the following groups where available:

- Different flap type (if >3 studies describing specific flap types)
- Venous vs. Arterial Doppler probe placement
- Different anatomic locations (if >3 studies describe the same anatomic locations)

Formatted: Bulleted + Level: 1 + Aligned at: 0.25" + Indent at: 0.5"

Dissemination

The number of free flaps that are compromised per year mean that improvements need to be made to monitoring protocols. It is possible that the Cook-Swartz Doppler may well represent a useful tool for such improvement. As such, the authors hope to disseminate the findings as widely as possible, irrespective of results as they add to wider corpora of information. The systematic review will be published in a peer-reviewed journal and include a number of recommendations as its conclusion based upon the evidence contained within. Given the wide range of specialities now utilising flaps, it will be presented at a wide range of national and international conferences. Updates of the review could be conducted as more information becomes available to guide best practice and further maintain the quality of evidence.

References:

1. Wong AK, Joanna Nguyen T, Peric M, Shahabi A, Vidar EN, Hwang BH, et al. Analysis of risk factors associated with microvascular free flap failure using a multi-institutional database. Microsurgery. 2014.
2. Schmulder A, Gur E, Zaretski A. Eight-year experience of the Cook-Swartz Doppler in free-flap operations: microsurgical and reexploration results with regard to a wide spectrum of surgeries. Microsurgery. 2011;31(1):1-6.
3. Liu Y, Zhao YF, Huang JT, Wu Y, Jiang L, Wang GD, et al. Analysis of 13 cases of venous compromise in 178 radial forearm free flaps for intraoral reconstruction. Int J Oral Maxillofac Surg. 2012;41(4):448-52.
4. Hidalgo DA, Jones CS. The role of emergent exploration in free-tissue transfer: a review of 150 consecutive cases. Plast Reconstr Surg. 1990;86(3):492-8; discussion 9-501.
5. Ali R, Bernier C, Lin YT, Ching WC, Rodriguez EP, Cardenas-Mejia A, et al. Surgical strategies to salvage the venous compromised deep inferior epigastric perforator flap. Ann Plast Surg. 2010;65(4):398-406.

6. Yu P, Chang DW, Miller MJ, Reece G, Robb GL. Analysis of 49 cases of flap compromise in 1310 free flaps for head and neck reconstruction. Head Neck. 2009;31(1):45-51.
7. Chen K-T, Mardini S, Wei F-C. Intraoperative Vascular Findings Predict Salvage Outcome in Free Flaps with Circulatory Compromise. J Reconstr Microsurg. 2006;22(07):A020.
8. Utley DS, Koch RJ, Goode RL. The failing flap in facial plastic and reconstructive surgery: role of the medicinal leech. Laryngoscope. 1998;108(8 Pt 1):1129-35.
9. Bibbo C, Fritsche T, Stemper M, Hall M. Flap infection associated with medicinal leeches in reconstructive surgery: two new drug-resistant organisms. J Reconstr Microsurg. 2013;29(7):457-60.
10. Dabb RW, Malone JM, Leverett LC. The use of medicinal leeches in the salvage of flaps with venous congestion. Ann Plast Surg. 1992;29(3):250-6.
11. Smit JM, Zeebregts CJ, Acosta R, Werker PM. Advancements in free flap monitoring in the last decade: a critical review. Plast Reconstr Surg. 2010;125(1):177-85.
12. Rozen WM, Enajat M, Whitaker IS, Lindkvist U, Audolfsson T, Acosta R. Postoperative monitoring of lower limb free flaps with the Cook-Swartz implantable Doppler probe: A clinical trial. Microsurgery. 2010;30(5):354-60.
13. Jallali N, Ridha H, Butler PE. Postoperative monitoring of free flaps in UK plastic surgery units. Microsurgery. 2005;25(6):469-72.
14. Dragu A, Linke R, Kuwert T, Unglaub F, Kneser U, Stürzl M, et al. Tc-99m Sestamibi SPECT/CT as a New Tool for Monitoring Perfusion and Viability of Buried Perforator Based Free Flaps in Breast Reconstruction After Breast Cancer. Clin Nucl Med. 2010;35(1):36-7 10.1097/RLU.0b013e3181c614d.
15. Top H, Sarikaya A, Aygit AC, Benlier E, Kiyak M. Review of monitoring free muscle flap transfers in reconstructive surgery: role of 99mTc sestamibi scintigraphy. Nucl Med Commun. 2006;27(1):91-8.
16. Lin SJ, Nguyen MD, Chen C, Colakoglu S, Curtis MS, Tobias AM, et al. Tissue oximetry monitoring in microsurgical breast reconstruction decreases flap loss and improves rate of flap salvage. Plast Reconstr Surg. 2011;127(3):1080-5.
17. Jyranki J, Suominen S, Vuola J, Back L. Microdialysis in clinical practice: monitoring intraoral free flaps. Ann Plast Surg. 2006;56(4):387-93.
18. Smit JM, Whitaker IS, Liss AG, Audolfsson T, Kildal M, Acosta R. Post operative monitoring of microvascular breast reconstructions using the implantable Cook-Swartz doppler system: a study of 145 probes & technical discussion. J Plast Reconstr Aesthet Surg. 2009;62(10):1286-92.
19. Swartz WM, Jones NF, Cherup L, Klein A. Direct monitoring of microvascular anastomoses with the 20-MHz ultrasonic Doppler probe: an experimental and clinical study. Plast Reconstr Surg. 1988;81(2):149-61.
20. Rozen WM, Chubb D, Whitaker IS, Acosta R. The efficacy of postoperative monitoring: a single surgeon comparison of clinical monitoring and the implantable Doppler probe in 547 consecutive free flaps. Microsurgery. 2010;30(2):105-10.
21. Paydar KZ, Hansen SL, Chang DS, Hoffman WY, Leon P. Implantable venous Doppler monitoring in head and neck free flap reconstruction increases the salvage rate. Plast Reconstr Surg. 2010;125(4):1129-34.

22. Kind GM, Buntic RF, Buncke GM, Cooper TM, Siko PP, Buncke HJ, Jr. The effect of an implantable Doppler probe on the salvage of microvascular tissue transplants. Plast Reconstr Surg. 1998;101(5):1268-73; discussion 74-5.
23. Pryor SG, Moore EJ, Kasperbauer JL. Implantable Doppler flow system: experience with 24 microvascular free-flap operations. Otolaryngol Head Neck Surg. 2006;135(5):714-8.
24. Poder TG, Fortier PH. Implantable Doppler in monitoring free flaps: a cost-effectiveness analysis based on a systematic review of the literature. Eur Ann Otorhinolaryngol Head Neck Dis. 2013;130(2):79-85.
25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
26. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009) [updated 01 July 201322 August 2013]. Available from: http://www.cebm.net/?o=1025.
27. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
28. Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011. Available from: www.cochrane-handbook.org.
29. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002.