ANGLIA RUSKIN UNIVERSITY

FACULTY OF HEALTH, EDUCATION, MEDICINE AND SOCIAL CARE

THE USE OF THE PEAK PLASMABLADE IN DIEP/MS-TRAM BREAST RECONSTRUCTION SURGERY COMPARED TO CONVENTIONAL DIATHERMY - a single centre, double blinded randomised controlled trial

THESSA REBECCA FRIEBEL

A thesis in partial fulfilment of the
requirements of Anglia Ruskin University
for the degree of Doctor of Medicine by Research

This research project was carried out in collaboration with the Mid Essex Hospital Services NHS Trust, Broomfield Hospital

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ABSTRACT

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DOCTOR OF MEDICINE BY RESEARCH

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Introduction: Electrosurgery makes dissection with simultaneous haemostasis possible. Inadvertently produced heat can cause injury to the surrounding tissue that may result in wound healing problems and an increased rate of seroma formation. The PEAK PlasmaBlade™ (PPB) is a new electrosurgery device which may overcome this by having the ability to operate on a lower temperature, therefore reducing collateral thermal damage.
Method: A double blinded, single centre, randomised controlled trial was conducted, including a 108 abdominally based free flap breast reconstruction patients who had their flap raise performed with either the PPB (n=56) or conventional diathermy (n=52). Data were collected during their in-patient stays and at the 2- and 6-week clinic follow-up appointments. The primary outcome value for which the study was powered was the number of days the abdominal drains were required. For statistical analysis the independent t-test, Mann-Whitney U test, Pearson Chi-Square test and Fisher's Exact test were used. Uni- and multivariable regression were used to identify and correct for predictors and confounders.
Results: Baseline characteristics were similar between the groups, except for a significantly lower flap weight in the PPB group for which was corrected. The median number of days the drains were required, was 6.0 (Interquartile Range (IQR) 5.0 – 8.8) days for the diathermy and 5.0 (IQR 4.0 – 8.0) days for PPB, this was not significant (p=0.48). Median amount of drain fluid was similar with 342.5 mL (IQR 233.8 – 618.8) in the diathermy and 355.0 mL (IQR 228.8 – 532.5) in the PPB group (p=0.68). In recovery, post-operative pain scores were significantly higher in the PPB group (2/10 vs 4/10, p=0.002). Three pro-inflammatory cytokine in the drain fluid showed a trend towards lower values in the PPB group on day 0,1 and 2 but did not reach statistical significance. Complications were similar between the groups (p>0.24). At the 2-week follow-up appointment there was a tendency towards less abdominal seromas on abdominal ultrasound in the PPB group (70.6% vs 54.5%, p=0.09) which were significantly smaller (62.8cm^3 (IQR 22.0 – 110.0) vs 45.6cm^3 (IQR 16.8 – 97.9), p=0.04). Due to spontaneous re-absorption presence and size of the identified seromas did not significantly differ anymore at the 6-week follow-up appointment.
Conclusion: Abdominally based free flap harvest performed with the PPB did not result in a significant reduction of drain requirement time, total output or inflammatory cytokines. Higher pain scores immediately post-operatively were recorded in the PPB group but could be the consequence of other factors. The abdominal ultra-sound performed at the 2-week follow-up appointment showed a tendency towards less seroma collections which were significantly smaller in the PPB group. Therefore, the PEAK PlasmaBlade™ device could reduce early post-operative seroma formation.

Key words: Electrosurgery, Conventional diathermy, PEAK PlasmaBlade™, Abdominally based free flap, Drain, Seroma.

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LIST OF ABBREVIATIONS

ABC	Argon Beam Coagulation
AC	Alternating Current
AIRE	Abdominal Inflammatory Response Evaluation
AJCC	American Joint Committee on Cancer
Amps	Amperes
ANC	Axillary Node Clearance
APC	Argon Plasma Coagulation
ARCTU	Anglia Ruskin Clinical Trial Unit
ARU	Anglia Ruskin University
BAAPS	British Association of Aesthetic Plastic Surgery
BIA-ALCL	Breast Implant Associated - Anaplastic Large Cell Lymphoma
BMI	Body Mass Index
BRCA	Breast Cancer
BREAST-Q	Breast Questionnaire
CADTH	Canadian Agency for Drugs and Technologies in Health
CCL2	C-C motif ligand 2
CD	Cluster of Differentiation
CE	Conformite Européene or Conventional Electrosurgery
CEM	Cumulative Number of Equivalent Minutes
CHIPPS	Children's and Infants' Postoperative Pain Scale
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
Cm	Centimetre
Coag	Coagulation
CRF	Case Report Form
CSF	Colony-Stimulating Factors
CT	Computed Tomography
CTA	Computed Tomography Angiography
D	Dalton
DC	Direct Current
DIEA/V	Deep Inferior Epigastric Artery/ Vein
DIEP	Deep Inferior Epigastric Perforator
Dr	Doctor
DVT	Deep Venous Thrombosis
EA	Elective Abdominoplasty
ECM	Extracellular Matrix Proteins
ED	Emergency Department
EGF	Epidermal Growth Factor
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FMI	Ferromagnetic Induction
FREP	Faculty of Medical Science Research Ethics Panel
FU	Follow-Up
G	Gram
GRS	Graphic Rating Scale
Gy	Gray
HDU	High Dependency Unit
HER-2	Human Epidermal Growth Receptor-2
HR	Hazard Ratio
Hz	Hertz
I	Current
IBM	International Business Machines
iBRA	Implant Breast Reconstruction Evaluation

ID	Identification
IFN	Interferon
Ig	Immunoglobulin
IGAP	Inferior Gluteal Artery Perforator
IGF	Insulin-Like Growth Factor
IL	Interleukins
ITA	Internal thoracic artery
IQR	Interquartile Range
IRAS	Integrated Research Application System
K	Kelvin
kDa	Kilodalton
L	Litre
LASER	Light Amplification by Stimulated Emission of Radiation
LD	Latissimus Dorsi
LDD	Least detectable dose
LLC	Limited Liability Company
LLOQ	Lower Limit of Quantification
LTD	Lateral Thermal Damage
Ltd	Limited Company
Max	Maximum
MCP	Monocyte Chemotactic Protein
MDT	Multidisciplinary Team
MEHT	Mid Essex Hospital Trust
MG	Matthew Griffiths
mg	milligram
Min	Minute
MIP	Macrophage Inflammatory Protein
mL	millilitre
mm	millimetre
M&M	Material and Methods
MPE	Monopolar Electrocautery
MS-TRAM	Muscle Sparing - Transverse Rectus Abdominis Myocutaneous
MRI	Magnetic Resonance Imaging
N	Population size
n	Sample size
ng	nanogram
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NPQ	National Practice Questionnaire
NRS	Numerical Rating Scales
OR	Oestrogen Receptor
OR	Odds Ratio
P-value	Probability Value
Pa	Pascal
PAF	Platelet-Activating Factor
PDGF	Platelet-Derived Growth Factor
PE	Pulmonary Embolism
PEAK	Pulsed-electron Avalanche Knife
pg	pictogram
PGMICTU	Post Graduate Medical Institute Clinical Trials Unit
PPB	PEAK PlasmaBlade™
PR	Progesterone Receptor
PRECISE	PEAK PlasmaBlade™ vs. traditional Electrosurgery in abdominoplasty
R	Resistance or Universal gas constant
R&D	Research and Development

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
Ref	Reference
RF	Radio Frequency
SC	Cold Scalpel
Sc	Subcutaneous
SD	Standard Deviation
SGAP	Superior Gluteal Artery Perforator
SIEA	Superficial Inferior Epigastric Artery
SLNB	Sentinel lymph node biopsy
SPSS	Statistical Package for the Social Sciences
St.	Saint
T	Temperature
t	Time
TDA/V	Thoracodorsal artery/vein
TED	Thromboembolism deterrent
TENALEA	Trans European Network for Clinical Trials Services
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
TNM	Tumour/Node/Metastasis
TRAM	Transverse Rectus Abdominis Myocutaneous
TUG	Transverse Upper Gracilis
UHS	Ultracision Harmonic Scalpel
UK	United Kingdom
US	United States
USS	Ultrasound Scan
V	Voltage
VAS	Visual Analogue Score
VR	Venkat Ramakrishnan
Vs	Versus
W	Watt (unit of power)
WLE	Wide Local Excision
Yr.	Year
ºC	Degree Celsius

CHAPTER 1: INTRODUCTION

1.1 Breast cancer

Breast cancer is caused by malignant cells in the breast (Figure 1). It is like all cancers characterised by uncontrolled division, abnormal growth and the ability to invade normal local tissue and spread to other sites in the body (metastasis), like lymph nodes (axillary/ internal mammary), lungs, bones, skin and soft tissue (Davies, 2012).

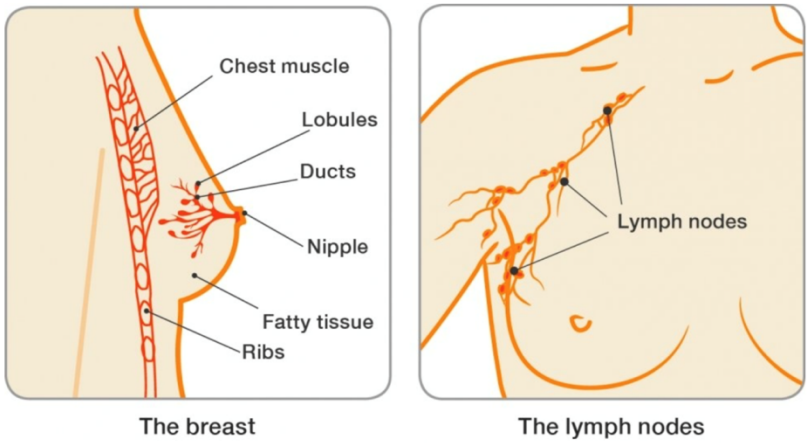


Figure 1 The breast and associated lymph nodes (Breast Cancer Care, 2016)

The majority of breast cancers (70-80%) originate from the ductal units of the breast (ductal carcinoma), with several subtypes (medullary, papillary, tubular and mucinous). The remaining 20% arise from the glandular tissue (lobular carcinoma) (Davies, 2012).

Breast tumours are classified according to the tumour/node/metastasis (TNM) classification (Davies, 2012).

1.1.1 History of breast cancer

The ancient Egyptians were the first to document surgery for breast cancer between 3000 and 2500 before Christ (Champaneria, Wong, Hill, & Gupta, 2012). Due to poor understanding of the human anatomy surgical treatment was surrounded by great controversy until the 19thCentury (Champaneria et al., 2012). Jean Louis Petit was the first to unify the surgical eradication of breast cancer by removing parenchymal breast tissue, chest muscle and lymph nodes (Champaneria et al., 2012). Between 1889 and the 1970s "*The Halsted Radical Mastectomy*" was the standard, consisting of an *en bloc* resection of the breast with underlying pectoral muscles and ipsilateral axillary lymph nodes (Figure 2). Wounds were closed under high tension or left to heal by secondary intention, as it was believed to decrease tumour dissemination (Champaneria et al., 2012).

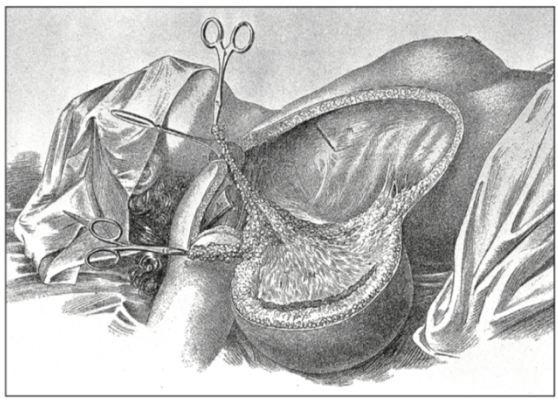


Figure 2 Drawing of a radical mastectomy, consisting of the surgical removal of all breast tissue with overlying skin, muscles and lymph nodes. By William Hasted in 1924, (Newmark, 2016).

In the 20th Century radical surgeries for breast cancer were questioned, which led to the development of breast conserving therapies. Modern prospective randomised controlled trials have confirmed that the extent of the mastectomy does not influence survival and also deemed breast reconstruction as safe, not compromising the cancer treatment (Champaneria et al., 2012). The introduction of the skin-sparing mastectomy in combination with immediate breast reconstruction in 1991, have greatly improved aesthetic results (Champaneria et al., 2012).

1.1.2 Incidence of breast cancer

In the United Kingdom one in seven women develops breast cancer within their lifetime. Fortunately, the survival rates have almost doubled over the last 40 years. Currently nearly eight in ten (78%) woman diagnosed with breast cancer in England and Wales survive their disease for ten years or more (Cancer research UK, 2017). The incidence increases with age, with 80% occurring in women over age of 50 years (Davies, 2012). Other risk factors for breast cancer are early menarche, late menopause, no or late pregnancy, being overweight, lack of exercise, alcohol consumption and prolonged use of exogenous hormones (hormone replacement therapy and/ or contraceptive pill) (Cancer research UK, 2017; Davies, 2012). Patients with the gene mutation BRCA-1 or BRCA-2 have an increased risk of 40 – 65% to develop breast cancer by the age of 70 (Cancer research UK, 2017; NHS, 2016).

1.1.3 Diagnosis of breast cancer

According to National Institute for Health and Care Excellence (NICE) guidelines (2016), all patients either presenting with symptoms such as a palpable swelling, breast skin changes or nipple discharge, or picked up through the NHS breast screening programme should be referred to a specialist breast clinic for triple assessment. This consists of: clinical history and examination, radiology (ultrasound investigation and/ or a mammogram) and pathology (biopsy from area of concern). Each component is scored ranging from 1 (benign) to 5 (malignant) (Jeevan et al., 2014; NICE, 2016). Following the assessment, each patient is discussed at a multidisciplinary team (MDT) meeting to confirm the diagnosis and treatment plan. This team consists of oncological breast surgeons, medical oncologists, radiologist, pathologist, psychologist and a specialist breast care nurse. In case of a cancer diagnosis important factors in the treatment decision-making process are tumour size, lymph node status, hormone receptor status (oestrogen receptor (OR), progesterone receptor (PR) and human epidermal growth receptor-2 (HER-2)), general health and wishes of the patient (Breast Cancer Care, 2016; Davies, 2012; Petit et al., 2012).

1.1.4 Treatment of breast cancer

Breast cancer can be treated surgically by completely removing the primary tumour and affected axillary lymph nodes. This can either be by breast conserving wide local excision (WLE; 70-75% of cases which is usually followed by post-operative radiotherapy) or mastectomy (25-30% of cases), where the entire breast is removed. To stage the axilla a sentinel lymph node biopsy (SLNB) can be performed, leading to higher accuracy compared to previous axillary sampling and less morbidity compared to axillary node clearance (ANC). The sentinel lymph node is the first node the tumour drains to and would usually be affected first. The node is identified using blue dye and a radioactive colloid suspension, surgically removed and histologically tested (Davies, 2012).

Radiotherapy, hormone therapy, biological therapy and (neoadjuvant-) chemotherapy are all forms of adjuvant treatment available for breast cancer patients. Their aim is to reduce loco-regional and distant recurrence to improve overall survival (Davies, 2012). The number of patients receiving adjuvant treatment has increased over the years, therefore the short- and long-term side-effects such as wound healing problems, skin fibrosis, myelo-suppression, cardiac toxicity and increased risk of thromboembolisms should not be neglected when planning breast reconstruction (Cancer research UK, 2017; Shapiro & Recht, 2001).

1.1.5 Conclusion

Breast cancer is very common, with currently 1 in 7 woman developing the disease within their lifetime (Cancer research UK, 2017). Due to improvements in diagnosis and (adjuvant) treatment of the disease, currently 78% of woman diagnosed with breast cancer in England and Wales survive their disease for 10 years or more (Cancer research UK, 2017). Despite a dramatic decrease in radicalism of the surgical treatment, still 25-30% of patients will require a mastectomy leading to significant asymmetry (Davies, 2012). Breast reconstruction can help improve quality of life in breast cancer survivors (Zhang et al., 2017; Zhong et al., 2012) and

is increasingly considered to be an important part of breast cancer management (Champaneria et al., 2012). The following chapter will discuss the history and different types of breast reconstruction.

1.2 Breast reconstruction

Even though the radicalism of surgical treatment of breast cancer has dramatically decreased, both breast conserving surgery and mastectomy can result in significant asymmetry between the breasts (Figure 3) (Petit et al., 2012). This can have a negative impact on a woman's self-image, psychology, relationships/ sexuality and quality of life (Zhang et al., 2017; Zhong et al., 2012). Due to concerns regarding oncological safety, breast reconstruction did not gain wide acceptance until the mid 1900s (Champaneria et al., 2012). The aim of breast reconstruction is to restore shape and symmetry by using the opposite side as a reference point and is increasingly considered as an important component of breast cancer management (Champaneria et al., 2012).

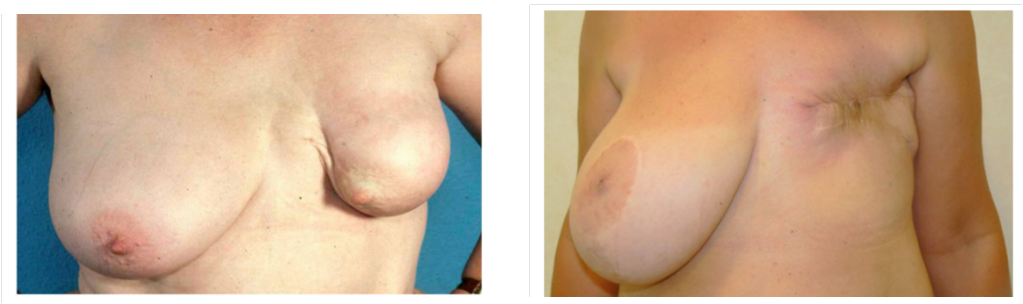


Figure 3 Significant asymmetry after breast conserving therapy (left) and mastectomy (right) (Petit et al., 2012)

An external prosthesis can be used after a mastectomy, but they are heavy, can slip and often compromise the patients' freedom to wear a variety of clothing which can lead to psychological stress for cancer survivors. Nowadays most patients are offered surgical breast reconstruction by either using an implant, the patient's own tissue (autologous) or a combination of both. Relative contraindications are significant anaesthetic risk factors or metastatic disease. Usually several operations are needed to complete the reconstruction process (Ahmed, Snelling, Bains, & Whitworth, 2005). Reconstruction can either be done immediately (at time of cancer surgery) or delayed (after adjuvant treatment). Immediate reconstruction has got advantages such as reduced costs, less psychological morbidity and superior cosmetic result (Ahmed et al., 2005). It has proven to be oncological safe as it does not increase the incidence

of local recurrence or distant metastases, neither does it affect the delivery of post reconstruction radiotherapy (Petit et al., 2012; See & Farhadi, 2018; Zhang et al., 2017).

1.2.1 Implant-based reconstruction

The National Mastectomy and Breast Reconstruction Audit published in 2011 included 16,485 mastectomy patients across England, Wales and Scotland. Twenty-one percent (n=3,389) underwent immediate breast reconstruction, which was most commonly with an implant or tissue expander (n=1,246, 37%). In the United Kingdom implant-based reconstruction is performed by both plastic and oncoplastic surgeons (Jeevan et al., 2014).

1.2.1.1 History of implant-based reconstruction

Plastic surgeon Thomas Cronin and his resident Frank Gerow were the first to develop silicone breast implants for cosmetic surgery with the Dow Corning Corporation in 1961 (Kaya & Serel, 2013). Unfortunately, these devices had a high failure rate, causing silicone leakage leading to painful deforming capsular contractions (Champaneria et al., 2012). These complications and public's concern of silicone implants causing cancer and certain autoimmune diseases made the American Food and Drug Administration (FDA) in 1992 restrict the use of silicone implants to breast reconstruction, replacement of previous defective implants and limited controlled trials (Champaneria et al., 2012). These restrictions were not applied in Europe (Kaya & Serel, 2013). During the 14-year embargo on silicone devices, saline filled implants dominated the U.S. market as they were FDA-approved. The ban was reversed in November 2006 after studies had shown silicone implants (Figure 4) to be safe and effective (Champaneria et al., 2012; Kaya & Serel, 2013).

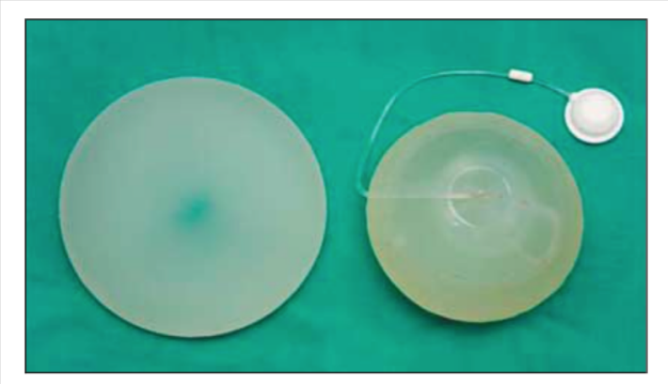


Figure 4 Silicone breast implant (left), tissue expander with remote port (right) (Ahmed et al., 2005)

Tissue expanders (inflatable implants, Figure 4) play an important role in breast reconstruction and were first presented in 1982 by Chedomir Radovan (Champaneria et al., 2012). After surgical implantation, they can gradually be inflated, stretching the overlying skin and muscle to the desired size. Expansion through an integrated or remotely positioned port can take a few months. By over-expansion a degree of ptosis can be created. Depending on the type of tissue expander, they can either be left or replaced with a permanent implant (Champaneria et al., 2012; Kaya & Serel, 2013).

1.2.1.2 Types of implants

Currently there are a lot of different types, shapes and sizes of implants available (Table 1.2.1), from many different manufacturers (Petit et al., 2012). All implants have a silicone envelope with either a silicone gel- or sterile saline filling (Ahmed et al., 2005; Kaya & Serel, 2013).

Table 1.2.1 Types of breast implants

		Specifics	Advantage	Disadvantages
Content	Silicone gel-filled		- Soft consistency - More natural result	-Can leak silicone
	Saline filled	Valve to allow filling or filled by manufacturer		-More solid consistency -More palpable
Surface structure	Smooth		- softer feel - reduced risk of rippling	- Capsular contraction - Implant migration - Only round shape
	Textured	(nano) textured	-Prevent capsular contraction -Prevent implant migration	- Associated with BIA-ALCL - Double capsules - Firmer to touch
Shapes	Round	Identical horizontal and vertical length	- Rotation not a problem	
	Anatomic- / Tear-drop shaped	Vertical length is greater than horizontal length	- More natural breast appearance	- Can rotate

BIA-ALCL = Breast Implant Associated – Anaplastic Large Cell Lymphoma

1.2.1.3 Patient selection

Implant based reconstruction is best suited for patients with small (≤500g) and minimally ptotic breasts. With larger ptotic breasts, reduction mammoplasty and mastopexy to the contra-lateral side can be used to improve symmetry. Complete coverage of the implant is imperative. This method of reconstruction has, compared to autologous reconstruction, got the benefit of a shorter general anaesthetic and hospital stay, without the need for an additional donor site with the risk of possible complications (Ahmed et al., 2005; Kaya & Serel, 2013). However for implant based reconstruction, secondary breast procedures and unplanned revisions within 3 years were significantly higher ($p<0.001$) in a retrospective cohort study including 15,154 woman undergoing immediate breast reconstruction with a tissue expander (70.5%), an immediate implant (11.3%) or autologous tissue (18.1%) (Fischer, Fox, Nelson, Kovach, & Serletti, 2015). Lagares-Borrego et al. (2016) published similar significantly higher number of

procedures ($p<0.001$) for implant based reconstruction in their prospective cohort study including 134 patients (67 expander/implant vs 67 autologous reconstructions) with a minimal follow-up of 5 years.

1.2.1.4 Reconstruction methods – single and two-stage reconstruction

The two main methods of breast reconstruction with implants are the single-stage reconstruction with a permanent expander or implant usually with the use of a mesh, or a two-stage reconstruction where the initial tissue expander is replaced with a permanent implant in a second surgery (Kaya & Serel, 2013; Lagares-Borrego et al., 2016). The two-stage procedure is most commonly practiced, due to the significantly higher risk of reconstructive failure and over-all complications after a single stage procedure. This was supported by the results of a systematic review and meta-analysis including 18 studies (14,840 cases), showing both significantly ($p<0.05$) more complications and implant loss in the one-stage group (Lee & Mun, 2016).

The implant breast reconstruction evaluation (iBRA) study was set up to evaluate the feasibility, design and conduct of a future trial in immediate implant-based breast reconstruction (Potter et al., 2019). The first part was a national practice questionnaire (NPQ) to describe the current practice of breast and plastic surgery units with regards to implant-based breast reconstruction (Mylvaganam et al., 2017). The response rates were 47% (67 of 144) of breast units and 26% (14 of 53) plastic units. The NPQ showed an increase in implant-based procedures, summarised selection criteria for different techniques and revealed that biological meshes are predominantly used (Mylvaganam et al., 2017). For the second part a prospective multi-centre study was performed including 2108 mastectomy patients undergoing immediate implant-based breast reconstruction, evaluating complications up to 3 months of the initial surgery. The study showed 78% of the reconstructions were single stage, using a biological (54%) or synthetic (12%) mesh, non-mesh sub-muscular or sub-fascial implants (9%), a dermal sling (21%), pre-pectoral implants (2%) or a combination of implants (4%). Due to the high number of one-stage reconstructions, the complication rates were higher

than recommended by the national standards, with 9% implant loss, 18% requiring re-admission, 18% return to theatre and 25% treatment for infection (Potter et al., 2019).

1.2.1.5 Implant-related complications

The most common early complication after implant reconstruction is loss of implant, occurring in about 6% of cases (Magill, Robertson, Jell, Mosahebi, & Keshtgar, 2017). This can be due to infection, mastectomy skin flap necrosis or wound healing problems. Capsular contraction is the most frequent late complication. It results from an immune response to the foreign body and leads to contraction of the fibroblastic capsule surrounding the implant causing a tight and painful reconstruction (Figure 5), occurring in about 19-25% of cases. Capsular contraction after breast reconstruction is classed according to the modified Baker classification (Bachour et al., 2018; Petit et al., 2012).

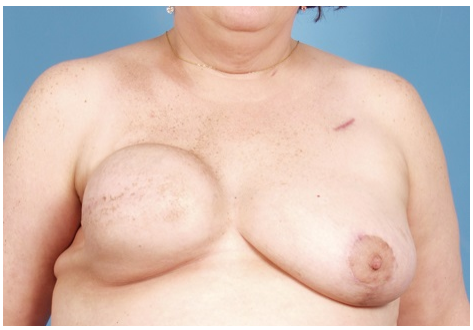


Figure 5 Capsular contraction of the right reconstructed breast (Hirsch, Seth, & Fine, 2012)

Other complications associated with implants are malposition, deflation, rupture and breast implant associated anaplastic large cell lymphoma (BIA-ALCL) (Ahmed et al., 2005; Kaya & Serel, 2013; Petit et al., 2012).

BIA-ALCL was first reported in 1997 and is a rare T-cell lymphoma associated with breast implants, in particularly those with a textured outer surface. An accurate risk assessment of BIA-ALCL has been elusive as both the number of actual cases and the prevalence of women with breast implants and implant type have not been registered accurately (Collett et al., 2019). The British Association of Aesthetic Plastic Surgery (BAAPS, 2019) estimates the incidence

between 1:20,000 to 1:60,000. It presents with late onset, rapid swelling of one breast due to a seroma. Removal of the capsule (capsulectomy) and implant is usually sufficient to treat the disease, but in more aggressive forms cytotoxic chemotherapy can be necessary (Santanelli di Pompeo & Sorotos, 2018).

1.2.2 Autologous breast reconstruction

In autologous breast reconstruction, the patient's own tissue is used to reconstruct the breast. To achieve this, a flap of tissue is transferred from a donor site to the anterior chest wall. This can either be as a pedicled flap, still attached to the original blood supply or as a free flap where the tissue is isolated, detached and anastomosed to a recipient blood vessel using microsurgery, which is only performed by plastic surgeons (Ahmed et al., 2005). Autologous reconstruction is considered the gold standard in breast reconstruction as it replaces like-with-like resulting in a soft, natural looking ptotic breast shape which is long lasting and does not require maintenance surgery like implant-based breast reconstruction. The lower abdominal tissue is most commonly used, due to its availability and low morbidity. Alternative donor sites are the buttocks, inner thighs, flanks and back (Table 1.2.2) (Kaya & Serel, 2013).

Table 1.2.2 Common autologous breast reconstruction flaps (Ahmed et al., 2005; Arnež, Pogorelec, Planinšek, & Ahčan, 2004; Petit et al., 2012)

LD flap	**Latissimus Dorsi Flap (pedicled flap) – Figure 7** • Donor side: Back Skin, fat and latissimus dorsi muscle • Blood vessel: Thoracodorsal artery/vein (TDA/V) Flap specific complications: seroma *Often a breast implant is needed to achieve adequate volume reconstruction*
Pedicled TRAM flap	**Pedicles Transverse Rectus Abdominus Myocutaneous Flap – Figure 8** • Donor side: Lower abdomen Skin, fat and rectus abdominis muscle tunnelled subcutaneously • Blood vessel: Deep superior epigastric artery/vein (DSAE/V) Flap specific complications: abdominal hernia, upper epigastric budge, seroma, fat necrosis

Free **(MS-)TRAM flap**	**Free (Muscle Sparing-) Transverse Rectus Abdominus Myocutaneous Flap – Figure 8** • Donor side: lower abdomen Skin, fat and portion of rectus abdominus • Blood vessel: deep inferior epigastric artery/vein (DIEA/V) Flap specific complications: abdominal hernia, seroma
DIEP flap	**Deep Inferior Epigastric Perforator Flap – Figure 9** • Donor side: lower abdomen Only skin and fat • Blood vessel: deep inferior epigastric artery/vein Flap specific complications: abdominal hernia, seroma
TUG flap	**Transverse Upper Gracilis Flap – Figure 10** • Donor side: upper inner thigh Skin, fat and gracilis muscle • Blood vessel: medial circumflex femoral artery/vein Flap specific complications: wound healing problems, seroma, asymmetry
IGAP flap	**Inferior Gluteal Artery Perforator Flap- Figure 11** • Donor side: lower buttock Skin and fat • Blood vessel: inferior gluteal artery/vein Flap specific complications: wound healing problems, seroma, asymmetry
SGAP flap	**Superior Gluteal Artery Perforator Flap – Figure 11** • Donor side: mid/ upper buttock Skin and fat • Blood vessel: superior gluteal artery/vein Flap specific complications: wound healing problems, seroma, asymmetry

1.2.2.1 History of autologous breast reconstruction

Attempts to reconstruct the breast in the early 1900s with the use of the contralateral breast and tubed flaps from the abdomen (Figure 6) were unsatisfying due to poor design, high donor site morbidity, the need for multiple stages and poor cancer survival rates. The first pedicled muscle flaps for breast reconstruction were the latissimus dorsi (described by Tansini in 1896 (Maxwell, 1980)) and pectoralis muscle (described by Ombredanne in 1906 (Teimourian & Adham, 1983)) (Table 1.2.3) (Champaneria et al., 2012; Rozen, Rajkomar, Anavekar, & Ashton, 2009). In the second part of 20th Century other donor sides were popularised for

single-stage procedures. Initially only pedicled flaps were used including the greater omentum and the lower abdomen (based on the deep superior epigastric artery) (Rozen et al., 2008).

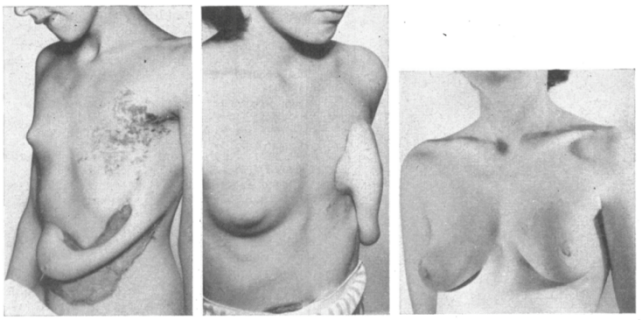


Figure 6 Stages of tubed pedicled flaps for early breast reconstruction (Gillies, 1959)

Daniel and Taylor (1975) introduced the free microvascular tissue transfer concept, which was first used for breast reconstruction by Fujino and colleagues (1975) using a free flap from the buttocks (Champaneria et al., 2012; Rozen et al., 2009). Donor site morbidity associated with muscle harvest in musculocutaneous flaps has been reduced over recent years following the advent of muscle-sparing perforator flaps such as the deep inferior epigastric perforator (DIEP) flap (Rozen et al., 2009).

Table 1.2.3 Important milestones in the evolution of autologous breast reconstruction (Champaneria et al., 2012; Rozen et al., 2009)	
1887	Pedicled contralateral breast (Verneuil)
1896	Pedicled latissimus dorsi myocutaneous flap (Tansini)
1895	Free lipoma transfer to breast (Czerny)
1906	Pectoralis minor muscle flap (Ombredanne)
1950	Composite tube pedicled contralateral breast (Yannilos)
1957	Pedicled racket shaped abdominal flap (Gillies and Millard)
1963	Pedicled greater omentum flap (Kiricuta)
1973	Pedicled, multistage gluteal myocutaneous flap (Orticochea)
1973	Free micro-vascular tissue transfer (Daniel and Taylor)
1975	Free superior gluteal artery myocutaneous flap (Fujino)
1977	Rectus abdominis myocutaneous flap (Mathes and Bostwick)
1979	Pedicled vertical rectus abdominis myocutaneous flap (Robbins)
1979	Rubens flap or deep circumflex iliac artery flap (Taylor)
1979	Free transverse rectus abdominis myocutaneous flap (Holström)
1982	Pedicled transverse rectus abdominis myocutaneous flap (Hartrampf et al)
1983	Extended deep inferior epigastric flap (Taylor)
1989	Free inferior gluteal artery myocutaneous free flap (Paletta et al)
1989	Free transverse rectus abdominis myocutaneous flap (Grotting et al)
1989	Free deep inferior epigastric artery perforator flap (Koshima and Soeda)
1992	Free transverse myocutaneous gracilis flap (Yousif et al)
1994	Muscle sparing deep inferior epigastric perforator flap (Allen and Treece)
1995	Pedicled latissimus dorsi perforator flap (Angrigiani et al)
1995	Free superior gluteal artery perforator flap (Allen and Tucker)
2004	Free inferior gluteal artery perforator flap (Guerra et al)

1.2.2.2 Latissimus dorsi (LD) flap

The latissimus dorsi myocutaneous flap is a pedicled flap based on the thoracodorsal blood vessels and was first described by Professor Ignio Tansini in 1896 (Champaneria et al., 2012; Maxwell, 1980). The flap fell out of favour after the Second World War but was re-discovered in 1976 by Neven Olivari (1979). It can reconstruct both skin and volume although usually a breast implant is needed to enhance the volume. It is a robust flap raised with a skin paddle, underlying subcutaneous fat and (part of) the latissimus dorsi muscle and transferred to the

anterior chest wall (Figure 7). Complications are usually donor site related, with large scars and seromas occurring in up to 80% of patients (Ahmed et al., 2005).

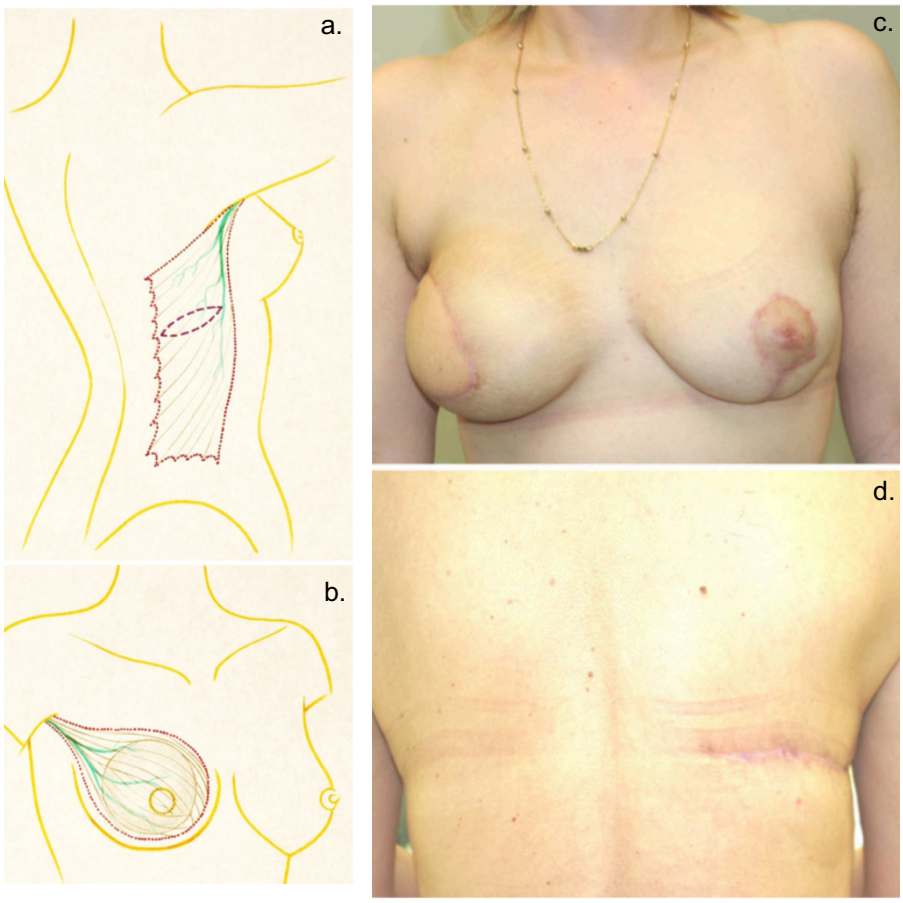


Figure 7 Latissimus dorsi flap a. Preoperative; b+c. Postoperative LD with implant; d. Donor site scar on the right side of the back (Petit et al., 2012)

1.2.2.3 Abdominal flaps – Transverse rectus abdominus (TRAM) flap, deep inferior epigastric perforator (DIEP) flap and superficial inferior epigastric artery (SIEA) flap

The first vertically pedicled musculocutaneous rectus abdominis flap for breast reconstruction was performed by Robbins (1979). In the same year, Holmstrom (1979) described the use of a transverse rectus abdominis myocutaneous (TRAM) flap for free-tissue transfer breast reconstruction. Hartrampf and colleagues (1982) subsequently published and popularised the pedicled TRAM flap, based on the superior epigastric artery. This flap used a vertically oriented rectus abdominis muscle but a horizontally oriented cutaneous skin paddle, resulting in a more cosmetically pleasing abdominal scar (Figure 8A). When it became apparent sacrificing the rectus abdominis muscle was not required, muscle sparing techniques were

sought to reduce abdominal wall morbidity. Taylor and colleagues (1983) only used the lower portion of the rectus muscle for his extended deep inferior epigastric flap (Champaneria et al., 2012). Koshima and Soeda (1989) first described the deep inferior epigastric perforator (DIEP) skin flaps without muscle sacrifice for a groin defect and the oral floor reconstruction. Allen and Treece (1994) used this DIEP flap for the first time in breast reconstruction. It is currently widely accepted to spare most of the rectus muscle, only sacrificing a cuff of muscle around the pedicle. Nahabedian et al. (2002) developed a classification system, ranking the amount of rectus abdominis muscle that was spared during the TRAM breast reconstruction (Table 1.2.4 and Figure 8) (Rozen et al., 2009).

Table 1.2. 4 Muscle sparing (MS) TRAM classification (Nahabedian et al., 2002)

MS-0 TRAM	Sacrifice of the full width (partial length) of the rectus muscle
MS-1 TRAM	Preservation of a lateral strip of muscle
MS-2 TRAM	Preservation of both lateral and medial strips while sacrificing only a small cuff of muscle around the perforators
MS-3 TRAM	Preserving the entire muscle (equivalent to a DIEP)

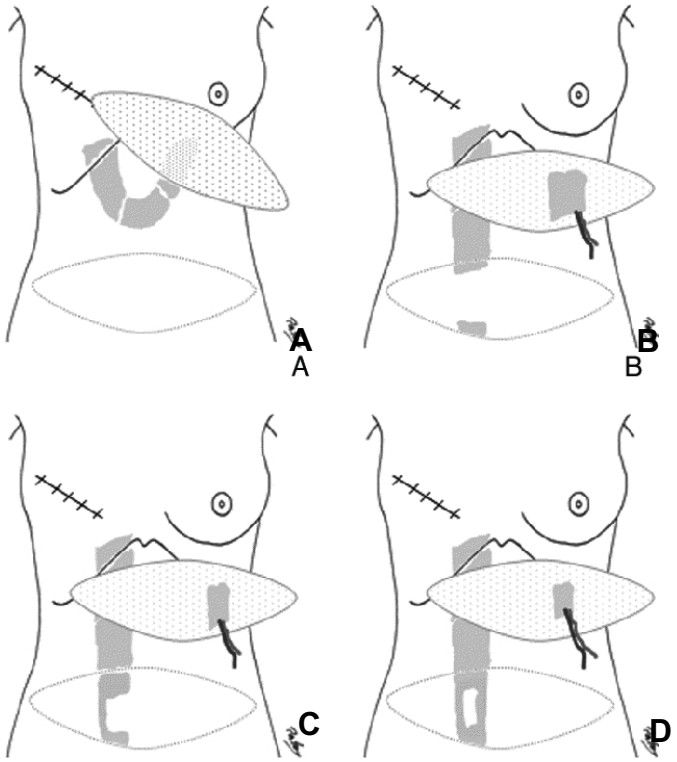


Figure 8 A) pedicled TRAM flap; B) MS-0 TRAM; C) MS-1 TRAM; D) MS-2 TRAM (Patricio Andrades et al., 2008)

Grotting (1991) first used the superficial inferior epigastric artery (SIEA) flap in 1991, which is the least invasive technique because it does not require opening of the anterior rectus sheath or any muscle dissection, as it is a supra-fascial cutaneous artery branching from the femoral artery. Disadvantages are the inconsistent, short vascular pedicle anatomy and small arterial diameter (Munhoz et al., 2011; Patel & Ramakrishnan, 2017).

The abdomen is the ideal source of tissue for autologous breast reconstruction as it is soft, easily shapeable and usually excessively available at a later age (Figure 9). Flap harvest also leads to the added benefit of improving the patients' abdominal contour, leaving them with a result similar to an abdominoplasty (tummy tuck) (Granzow, Levine, Chiu, & Allen, 2006; Rozen et al., 2009).

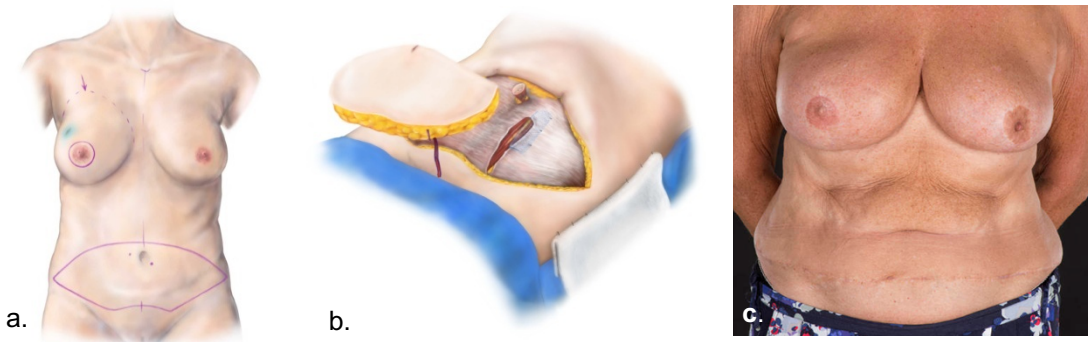


Figure 9 Deep inferior epigastric perforator flap. a. Preoperative markings; b. Raised DIEP flap; c. Postoperative result of right immediate reconstruction. *Drawings by Ms Julia Ruston.*

By preserving all or most of the rectus muscle with techniques such as the DIEP and SIEA flaps, the incidence of abdominal donor site weakness and complications has been greatly reduced, compared to the TRAM flap (Egeberg, Rasmussen, & Sorensen, 2012). Donor side weakness was evaluated by Blondeel at al. (1997) prospectively in 18 DIEP patients (mean follow-up of 17.8 months), comparing them to a control group (n=20) and a retrospective group of free TRAM flap breast reconstruction patients (n=20). Despite this only being a small study population it showed a significantly reduced exercise strength of the TRAM group compared to both DIEP and control group ($p<0.05$). Ten of the 12 DIEP patients examined with a CT or MRI scar had no muscle atrophy. The objective data was correlated to patient questionnaires, which also subjectively TRAM patients experience a reduced abdominal strength with a reduced ability to daily activities. Pre-operative mapping of the perforators with computed tomography angiography (CTA) has reduced the operating time and complication rate (Ghattaura et al., 2010; Rozen et al., 2008). Disadvantages of the free (MS)-TRAM and DIEP flap include an average operating time of 4-6 hours, 6-day hospital stay, 6-week recovery (Ahmed et al., 2005). Possible complications are (partial) flap failure (0.4-5%), haematoma (1-15%) , infections (1-12%), wound healing problems (12-39%), umbilical necrosis (2-3%) and an abdominal bulge (2.3-33%) or hernia (0-7.1%) (Lindenblatt, Gruenherz, & Farhadi, 2019; Schaverien & Butler, 2017). If the abdomen is insufficient in a thin patient or not usable after previous surgery alternative donor sites can be used for autologous breast reconstruction.

1.2.2.4 Transverse Upper Gracilis (TUG) flap

The first description of the free myocutaneous gracilis flap by Harii et al. (1976) for soft-tissue defect coverage (Rozen et al., 2009). Problems with the perfusion of the vertical skin paddle led to further anatomic studies. Yousif et al. (1992) published the presence of mainly transversely oriented perforators, which resulted in the use of the first transverse upper gracilis flap (Arnež et al., 2004; Patel & Ramakrishnan, 2017; Rozen et al., 2009). The harvested melon-slice shaped flap consists of skin, fat and part of the gracilis muscle. This is a true musculocutaneous flap supplied by the medial femoral circumflex system. Up to 400mg can be harvested from the medial upper thigh, making it suitable for reconstruction of small to medium sized breasts (Figure 10). Possible donors side complications are a low non-concealable scar, wound healing problems, infection, seroma, lymphedema and sensory changes (Patel & Ramakrishnan, 2017).

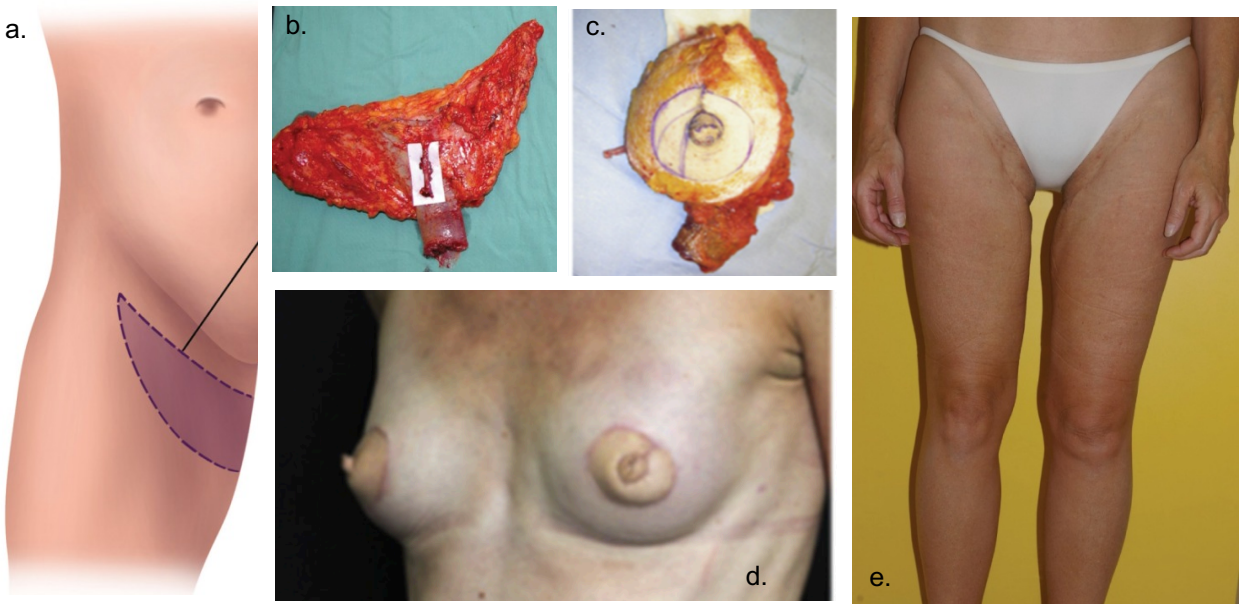


Figure 10 a. Preoperative marking TUG flap; b. Raised free TUG flap; c. Coned TUG flap with nipple reconstruction; d. Bilateral TUG breast reconstruction; e. Bilateral donor site scars (Buchel, Dalke, & Hayakawa, 2013; Patel & Ramakrishnan, 2017)

1.2.2.5 Superior/Inferior gluteal artery perforator (S/IGAP) flap

The gluteal region was first used for breast reconstruction by Orticochea (1973), where he transferred a musculocutaneous gluteal flap in 5 stages, using the volar forearm as a transport

medium (Champaneria et al., 2012; Rozen et al., 2009). Fujino et al. (1975) introduced a one stage free musculocutaneous based on the superior gluteal artery (Champaneria et al., 2012). From 1989 the inferior gluteal artery musculocutaneous free flap has been used in breast reconstruction. The perforator flaps concept in the buttocks area lead to the introduction of the superior and inferior gluteal artery perforator flaps (S/IGAP) (Figure 11) (Allen, 1998; Allen & Tucker, 1995; Rozen et al., 2009; Shaw, 1983). The main issues with these flaps are challenging perforator dissection, short vascular pedicle, recipient vessel discrepancy, exposure of the sciatic nerve and the need to turn the patient over during the procedure (Patel & Ramakrishnan, 2017).

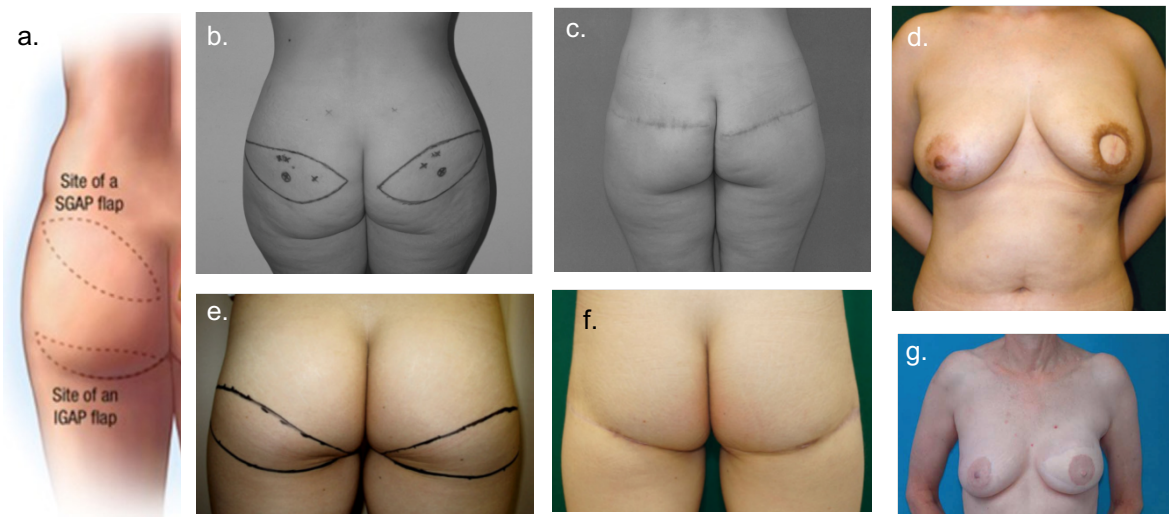


Figure 11 a. Markings of superior (b) and inferior (e) gluteal artery perforator flaps. Donor site scars after SGAP (c) and IGAP (f). Results after SGAP (d) and IGAP (g) (Anita T. Mohan & Saint-Cyr, 2015; Satake et al., 2015)

1.2.3 Combination of implant and autologous reconstruction

Sometimes a small implant is used if autologous tissue flaps are insufficient to achieve adequate volume reconstruction (Ahmed et al., 2005; Champaneria et al., 2012; Kaya & Serel, 2013). The downside of combining these two techniques is the patient experiences the worse of both worlds, having the donor side scar and long recovery of the flap combined with the need for maintenance surgery for the used implant.

1.2.4 Further procedures

Nipple reconstruction can be done at the initial breast reconstruction procedure but is usually done at a later stage. It has been shown patients satisfaction with their overall reconstruction is higher after nipple reconstruction has been completed (Momoh et al., 2012). Nipple reconstruction can either be achieved by a local flap or nipple sharing, in which a part of the opposite nipple is grafted to the reconstructed breast. The areola can be reconstructed with the help of tattooing.

Touch up operations can be done to improve the symmetry and cosmetics after breast reconstruction. Some examples are scar revisions, lipofilling for contour deformities and contra-lateral breast procedures such as reduction, mastopexy or augmentation (Rozen et al., 2009).

1.2.5 Breast reconstruction and radiotherapy

Radiotherapy uses ionizing radiation, which is delivered by external beam radiation to the target areas (chest wall and/ or lymph nodes). This causes irreversible damage to both malignant and healthy cells within the treated field, clinically leading to skin fibrosis, telangiectasia, skin thinning, pigmentation and reduced healing capacity (See & Farhadi, 2018). Due to same tumour control but fewer adverse effects most centres now give 40 Gy in 15 fractions over three weeks (Schaverien, Macmillan, & McCulley, 2013). The published benefit on overall survival of postmastectomy radiotherapy in patients with node-positive disease has resulted in an increase in its role as an adjunct in the breast cancer treatment (Cassidy et al., 2017; Everett, De Los Santos, & Boggs, 2018; Magill et al., 2017; McGale et al., 2014; Overgaard et al., 1997; Ragaz et al., 1997; Tendulkar et al., 2012). This has led to an increased number of patients requesting 1) immediate breast reconstruction with the need for post-mastectomy radiotherapy and 2) delayed reconstruction following previous irradiation (See & Farhadi, 2018). Despite the therapeutic advantages on overall-/ loco-regional recurrence and survival, post-reconstruction radiotherapy increases the risk of complications and can compromise the cosmetic outcome and patient satisfaction after breast reconstruction

(Ho, Hu, Mehrara, & Wilkins, 2017; Magill et al., 2017). Implant-based reconstruction has got a much higher risk of failure (18.7 - 32%) compared to autologous reconstruction (1.0 - 4.3%) (Ho et al., 2017; Jagsi et al., 2018; Schaverien et al., 2013; See & Farhadi, 2018). Also, the capsular contracture rates increase dramatically in case of pre- or post-operative radiotherapy with a systematic review and meta-analysis publishing an odds ratio of 10.21 (95% CI 3.74 to 27.89, $p<0.00001$) (Magill et al., 2017). Autologous reconstructions are less affected by radiotherapy and have a higher patient satisfaction and aesthetic outcome. Some degree of tissue shrinkage has been reported and significantly more patients develop fat necrosis after radiotherapy (OR 2.82, 95% CI 1.35 – 5.92, $p= 0.006$) but this usually does not require revision surgery (Schaverien et al., 2013). Jagsi et al. (2018) published a prospective multicentre cohort study reporting the impact of radiotherapy on complications and patient reported outcomes in 2247 breast reconstruction patients. After a two years follow-up, they reported 33.2% of irradiated patients who had received implant-based reconstruction experienced major complications (rehospitalisation or re-operation), compared to 17.6% of irradiated patients receiving autologous breast reconstruction. Failure rates at two years of irradiated implants were 18.7% compared to 1% of irradiated autologous reconstructions. The BREAST-Q patient-reported satisfaction in irradiated patients at 2 years was 63.5/100 after autologous reconstruction and only 47.7/100 after implant-based reconstruction.

1.2.6 Costs of breast reconstruction

The increased survival and public awareness have led to a continuous rise in the demand for surgical breast reconstruction after mastectomy from 15% in 2000 to 32% in 2011 in the US (Ho et al., 2017). The costs of breast reconstruction have a significant impact on the already under stress British National Health System (NHS).

A cost-effectiveness analysis from Grover et al. (2013) including 54 publications (n=7278) compared health effects, outcomes and complications up to 7 years postoperatively in five different breast reconstruction techniques. This study concluded autologous tissue

reconstruction techniques to be the most cost-effective options in both irradiated and non-irradiated patients.

Lagares-Borrego et al. (2016) compared the 2-year costs of the two-stage expander/ implant reconstruction with the autologous Deep Inferior Epigastic Perforator (DIEP) flap in 134 delayed breast reconstruction patients. They included costs of the procedure/labour costs, used materials, length of hospital-stay, number of consulting appointments and costs of additional interventions due to complications or for aesthetic retouches. Despite the initial higher costs of the DIEP reconstruction there was no significant difference between the total costs of both techniques. This can be attributed to the fact autologous reconstruction achieves great stability compared to implant reconstruction which tends to develop complications and other unfavourable outcomes leading to an unsuccessful reconstruction over time.

1.2.7 Conclusion

Due to an increased survival rate (Cancer research UK, 2017), proven oncological safety (Champaneria et al., 2012) and numerous studies demonstrating positive influence on emotional and psychological well-being (Jeevan et al., 2014; Rowland, Holland, Chaglassian, & Kinne, 1993; Zhang et al., 2017; Zhong et al., 2012) the demand for breast reconstruction has increased over recent years (Grover et al., 2013; Ho et al., 2017). Implant-based reconstruction is still most commonly performed also in the setting of radiotherapy, despite higher rates of complications, implant loss and revision surgery (Ho et al., 2017; Magill et al., 2017). Possible reasons for this are the initial higher costs of autologous breast reconstruction, the availability of resources (plastic surgeons performing microsurgery and theatre time), patient factors (age, co-morbidities, unavailable donor-site) and patient preference (more extensive surgery and recovery time) (Jagsi et al., 2018; See & Farhadi, 2018).

St. Andrew's Centre for Plastic Surgery and Burns in Broomfield Hospital, Chelmsford UK is one of the biggest regional specialist plastic surgery units in the United Kingdom, covering a

population of over 3.2 million people. The department performs over 300 autologous free flap breast reconstructions every year, which are mainly DIEP flaps. The increasing demand on the service and innovative character of the speciality are driving forces to keep looking for ways to improve efficiency and outcomes for abdominally based free flap breast reconstruction patients. The following chapter will go through the stages of wound healing with the aim to identify markers that can be used to quantify the amount of tissue damage inflicted during surgery.

1.3 Wound healing

An injury to the skin compromises its protective integrity and sets in motion a well-orchestrated response to heal the wound and eliminate the possible outside threats.

1.3.1 The skin

The skin is the largest organ of the human body and has many different functions, but most importantly provides a protective physical barrier from external factors to keep the internal systems safe (Gawkrodger, 2003).

1.3.1.1 Contents of the skin

The skin is made out of three layers, an epidermis, dermis and hypodermis (Figure 12). The avascular epidermis is further divided into five layers (from superficial to deep): stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. Keratinocytes, the main cells of the epidermis replicate in the basal layer, pushing up older cells while losing their nucleus and flattening off. A complete turnover cycle takes around 48 days. Essential appendages within the epidermis such as pilo-sebaceous units (hair follicle with associated sebaceous gland) and apocrine glands, contain epithelial stem cells which can differentiate into basal keratinocytes, making them essential in re-epithelization. The dermis is a tough supportive connective tissue matrix, containing blood vessels, lymphatics, nerves, skin appendages and different cells such as fibroblasts, dermal dendrocytes, macrophages and lymphocytes. There is an upper papillary dermis and a deeper and thicker reticular dermis. The hypodermis or subcutis is mainly built of loose connective tissue and fat (Gantwerker & Hom, 2012; Gawkrodger, 2003). The different layers of the skin vary in thickness depending on gender, age and anatomical site (Ye & De, 2017).

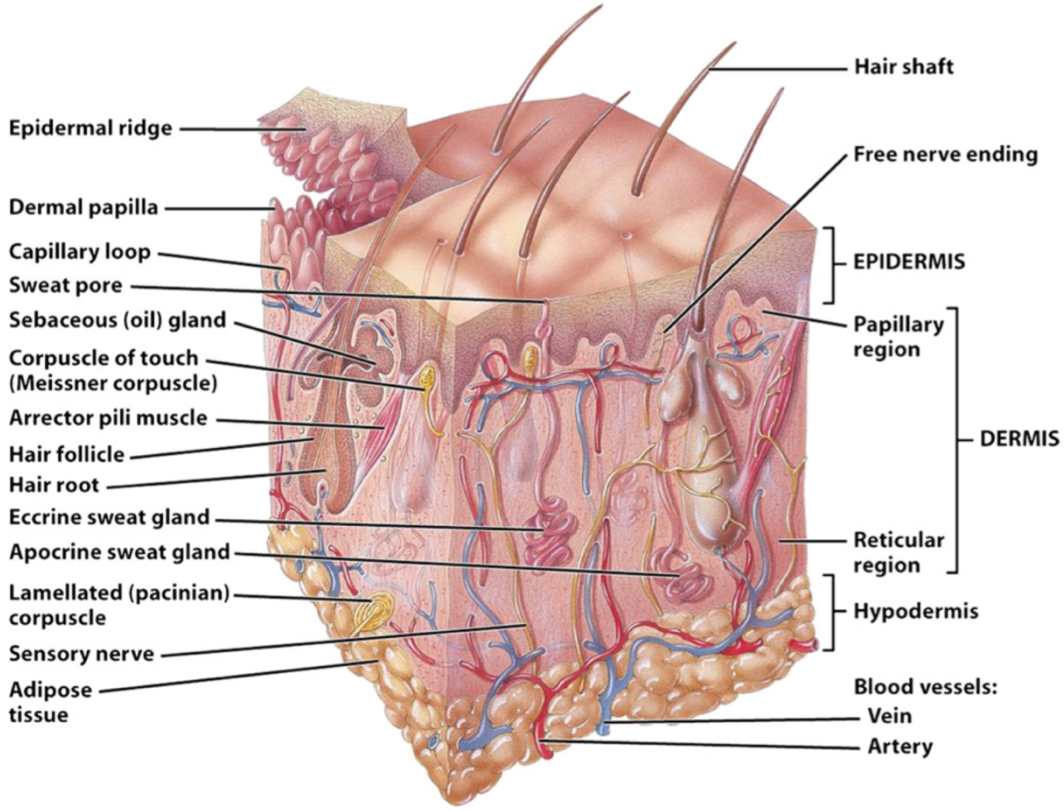


Figure 12 Sectional view of skin and subcutaneous layers (Gantwerker & Hom, 2012)

1.3.2 Stages of wound healing

Traditionally wound healing has been divided in four distinct phases:

- Haemostasis
- Inflammation
- Proliferation
- Maturation and remodelling

This division of the actually overlapping (Figure 13) stages of wound healing is arbitrary but allows easier description and evaluation.

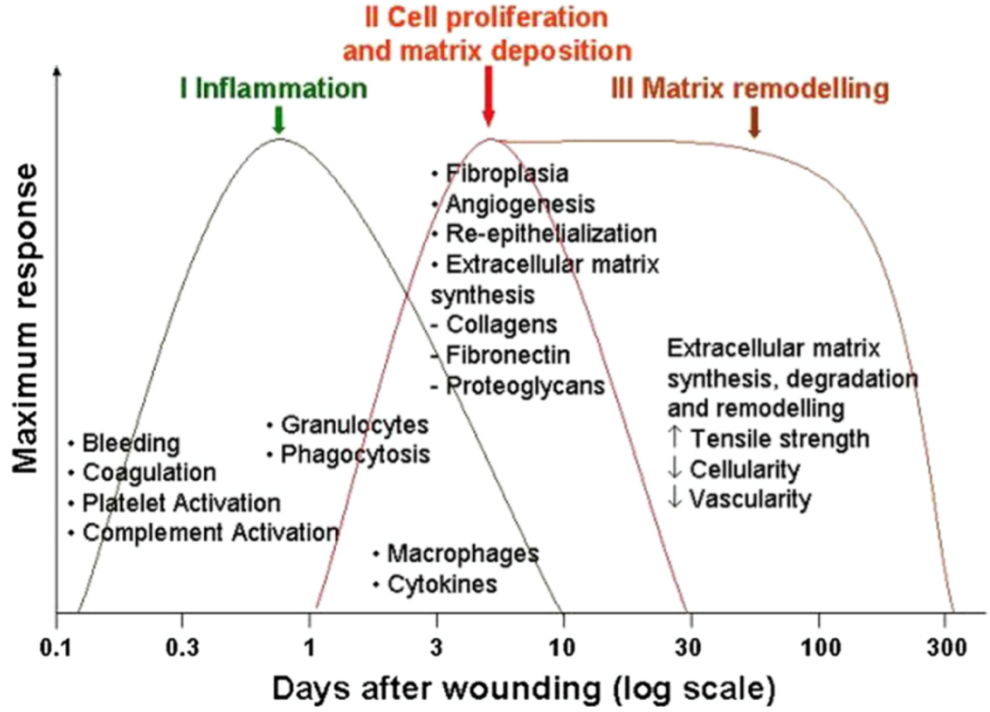


Figure 13 Time scale of four phases of wound healing (Gantwerker & Hom, 2012)

Haemostasis

This phase initiates within seconds to minutes of the initial injury disrupting the vascular endothelium. Platelets are key as they not only ensure initial haemostasis by activating the extrinsic and intrinsic coagulation cascades, but also release cytokines, hormones and chemokines to attract inflammatory cells and start the other phases of wound healing. Larger vessels vasoconstrict under the influence of vasoactive substances such as catecholamines and serotonin. Smaller vessels vasodilate to allow the entrance of red blood cells, leukocytes and plasma proteins. The formed clot made of collagen, platelets, thrombin and fibronectin not only serves as a scaffold for infiltrating cells but also releases and concentrate growth factors and cytokines to initiate the inflammatory response (Gantwerker & Hom, 2012).

Inflammation

The inflammatory phase is characterised by vasodilatation and increased vascular permeability, allowing the influx of neutrophils, lymphocytes and macrophages. The

neutrophils who arrive first onsite, attract the macrophages via by-products of their apoptosis. These and other phagocytic cells stay present until the end of the inflammatory phase, clearing debris and bacteria from the area. Macrophages produce numerous enzymes, such as collagenases to debride the wound, tumour necrosis factor (TNF) and interleukins (ILs) to stimulate fibroblasts and angiogenesis and transforming growth factor (TGF) which activates keratinocytes and fibroblasts. These macrophages are also key in the transition into the proliferative phase (Broughton, Janis, & Attinger, 2006a; Gantwerker & Hom, 2012).

Proliferation

This repair phase involves re-epithelization, capillary budding and granulation tissue formation. If the basement membrane has been damaged, re-epithelization occurs from stem cells in apocrine glands and buds of hair follicles. They differentiate into keratinocytes which then migrate over the wound edges and lay down a new basement membrane. Contact between keratinocytes, after the wound defect is filled in, inhibits further migration. Angiogenesis by endothelial cell migration and the formation of capillaries is essential for a sufficient nutrient supply and proper wound healing. Fibroblasts are key in granulation tissue formation as they transform into myofibroblasts which synthesize several extracellular matrix proteins (ECMs) such as fibronectin, glycosaminoglycans and collagens. Myofibroblasts also have the ability to contract, achieving wound contraction (Broughton, Janis, & Attinger, 2006b; Gantwerker & Hom, 2012).

Maturation and remodelling

This is the longest phase and results in the final appearance of the wound. The provisional ECMs and type III collagen is replaced with type I collagen, cells from previous phases go into apoptosis, granulating tissue involutes and excessive blood vessels retract. This phase requires more synthesis than lysis (Gantwerker & Hom, 2012).

1.3.3 Cytokines in wound healing

The initial response to trauma is largely coordinated by endogenous soluble mediators referred to as cytokines. They are produced by systemic immune cells and diverse cell types at the site of injury (Lin, Calvano, & Lowry, 2000). Cytokines can be classified into families based on their three-dimensional structure and binding receptors. Some of the key cytokines are interferons (IFNs), chemokines, lymphokines, interleukins (IL), colony-stimulating factors (CSF) and tumour necrosis factor (TNF) (Holdsworth & Gan, 2015; Tanaka & Kishimoto, 2014). They are made up of polypeptides or glycoproteins of molecular weight of 5 to 30 kilodalton and function predominantly within a short distance of their release by intracrine, autocrine and paracrine mechanisms. By binding to specific cellular receptors, they influence immune cell activity, differentiation, proliferation and survival. The activity of these pleiotropic mediators ultimately results in pro- and anti-inflammatory response at the site of injury aiding in wound healing (Henry & Garner, 2003; Lin et al., 2000).

The main cytokines related to (surgical) injury and inflammatory response are listed below:

Tumour necrosis factor-α (TNF-α)

TNF-α is one of the earliest and most potent mediators released after an injury or during an infection. It is primarily produced by T lymphocytes and monocytes/ macrophages. Despite a half-life of less than 20 minutes, TNF-α is able to elicit a significant metabolic and haemodynamic changes and activate cytokines further down the cascade. Other actions of TNF-α involve coagulation activation, stimulating the expression or release of adhesion molecules, platelet-activating factor (PAF), prostaglandin E2, glucocorticoids and eicosanoids (Lin et al., 2000).

Interleukin-1 (IL-1)

IL-1 is primarily released by endothelial cells and activated macrophages. Like TNF-α, at high dosages IL-1 can elicit a stage of haemodynamic decompensation. Low doses of both

cytokines can produce the same response, emphasizing the synergistic role in the inflammatory response. The half-life of IL-1 is only 6 minutes making it even more difficult to detect than TNF-α. By stimulating local prostaglandin activity in the anterior hypothalamus, it induces a febrile response after injury (Lin et al., 2000).

Interleukin-2 (IL-2)

IL-2 primarily promotes T lymphocyte proliferation, immunoglobulin production and the integrity of the gut barrier. Its half-life is less than 10 minutes. A transient immunocompromised state of the surgical patient can potentially be a consequence of diminished levels of IL-2 after major injuries or perioperative blood transfusions (Lin et al., 2000).

Interleukin-4 (IL-4)

IL-4 has a diverse influence on haematopoietic cell proliferation and is produced by activated T helper cells. It is important in antigen presentation, antibody-mediated immunity and induces B lymphocytes to produce predominantly IgG and IgE. IL-4 has got anti-inflammatory properties as it can down regulate the effects of IL-1, TNF-α, IL-6 and IL-8 on activated macrophages and increases their susceptibility to the effects of glucocorticoids (Lin et al., 2000).

Interleukin-6 (IL-6)

IL-6 is a multifunctional cytokine (Figure 14) but its key-functions are mediation of the physiologic acute phase response to injury and haematopoiesis. Production in a wide variety of non-immune and immune cell types is induced by tissue damage, triggering an alarm signal which activates the hosts defence mechanisms (Biffl, Moore, Moore, & Peterson, 1996). IL-6 is an early and sensitive marker of tissue damage and is considered to represent the extend of stress following surgery (Y. Kumagai et al., 2014). The increase is evident soon after injury and usually lasts for 24-48 hours but can persist longer in patients with more severe injuries (Volpin et al., 2014).

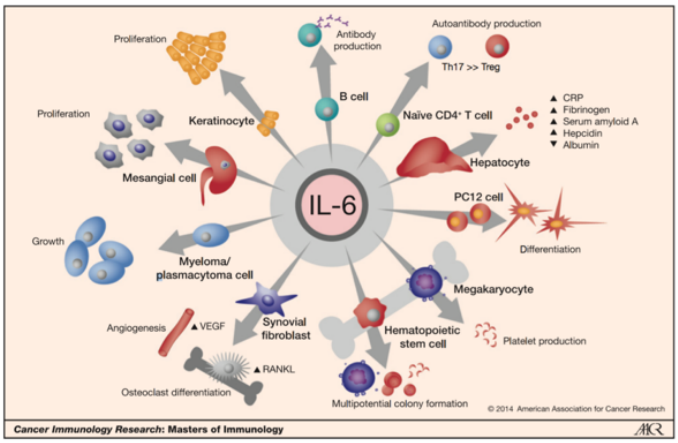


Figure 14 Pleotropic activity of IL-6 (Tanaka & Kishimoto, 2014).

Interleukin-8 (IL-8)

IL-8 is produced by phagocytes and mesenchymal cells exposed to tissue injury and is the main chemoattractant and potent activator of neutrophils (Baggiolini & Clark-Lewis, 1992; Lin et al., 2000).

Interleukin-10 (IL-10)

IL-10 is a potent anti-inflammatory cytokine which can attenuate the production of other inflammatory cytokines, thereby limiting the host's immune response preventing chronic inflammatory and autoimmune pathologies (Iyer & Cheng, 2012).

Interleukin-12 (IL-12)

IL-12 has a primary role in cell-mediated immunity and encourages the differentiation of T-helper cells. It also promotes coagulation and neutrophil activation, as well as the expression of both anti- and pro-inflammatory mediators (Lin et al., 2000).

Interleukin-13 (IL-13)

IL-13 modulates macrophage and selected B lymphocytes function. Along with IL-4 and IL-10, IL-13's end result is anti-inflammatory (Lin et al., 2000).

Interleukin-15 (IL-15)

IL-15 is macrophage-derived cytokine with potent autocrine regulatory features. Sharing receptor signalling components with IL-2, results in similar bioactivity in promoting lymphocyte activation and proliferation (Lin et al., 2000).

Interleukin-18 (IL-18)

IL-18 (previously known as interferon-γ-inducing factor) is a member of the IL-1 superfamily. This pro-inflammatory cytokine produced by activated macrophages is an important regulator of the innate and acquired immune responses (Gracie, Robertson, & McInnes, 2003).

Interferon-γ (IFN-γ)

IFN-γ is produced by activated human T helper lymphocytes and has an important role in activating circulating and tissue macrophages (Lin et al., 2000).

Macrophage Inflammatory Protein-1 alpha and beta (MIP-1 alpha and beta)

MIP-1 is produced mainly by macrophages, dendritic cells and lymphocytes. Their primary effects are chemotaxis and induction and modulation of the inflammatory response. They can also stimulate homeostasis (Maurer & von Stebut, 2004).

Monocyte Chemotactic Protein-1 (MCP-1)

MCP-1, also referred to as chemokine C-C motif ligand 2 (CCL2) belongs to the CC chemokine family. It is one of the important chemokines that regulates migration and infiltration of monocytes and macrophages (Deshmane, Kremlev, Amini, & Sawaya, 2009).

1.3.4 Growth factors in wound healing

Growth factors are proteins with a weight between 4000 and 60,000 Kilodalton (kDa). They modulate wound healing by stimulating non-hematopoietic cellular functions through

endocrine, paracrine, intracrine or autocrine mechanisms. Main effects are stimulation of protein production, matrix turnover, synthesis of extra cellular matrix and cell death. There are five superfamilies of growth factors namely, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF) and insulin-like growth factor (IGF) (Henry & Garner, 2003).

1.3.5 Levels cytokines in correlation to trauma

Biffl et al. (1996) published a literature review where they concluded IL-6 response to injury is uniquely consistent and relates to the magnitude of the insult after trauma, burns and elective surgery. Taniguchi et al. (1999) found a significant correlation between serum IL-6 and IL-10 levels and injury severity scores in 20 patients with chest and abdominal trauma. Those results were repeated by Stenseballe at al. (2009), also showing a significant correlation between injury severity scores in 265 trauma patients and their serum levels of IL-6 and IL-10 measured upon arrival and at 6, 12 and 24hours after admission. The same findings have been published for open vs closed elective procedures such as cholecystectomy, gastrectomy, colonic resection and aortobifemoral bypass surgery (Delgado et al., 2001; Grande et al., 2002; Haq et al., 2004; Hildebrandt et al., 2003; Jawa, Anillo, Huntoon, Baumann, & Kulaylat, 2011; Krog et al., 2016; Y. Kumagai et al., 2014; Reith, Kaman, Mittelkotter, Kilic, & Kozuschek, 1997; Schietroma et al., 2004; Schwenk, Jacobi, Mansmann, Bohm, & Muller, 2000).

1.3.6 Levels of inflammatory cytokines in drainage fluid

Levels of inflammatory cytokines in wound drainage fluid are higher compared to circulating levels in serum and are expected to be a better representation of interstitial levels (van der Heide, van der Kraan, Rijnberg, Buma, & Schreurs, 2010). Di Vita et al. (2005; 2006) published two papers measuring levels of several cytokines (IL-1, IL-6, IL-10) and growth factors in wound drainage fluid of ten patients after an incisional hernia repair on post-operative days 1

to 4. This showed the highest levels of all cytokines on day 1, decreasing over the following days.

Van der Heide et al. (2010) reported a significant increases of levels for almost all cytokines (IL-1, IL-2, IL,4, IL-5, IL-6, IL-7, IL-8, IL-12, IL-13, IFN-gamma, TNF-alpha and MCP-1) in drainage fluid samples taken after one and six hours post-operatively in 30 total hip replacement patients.

Özdogan et al. (2008) published an important paper for this thesis where they showed significantly higher levels of TNF-alpha in the drain fluid 24 hours after diathermy (n=18) dissection compared to the less traumatic scalpel (n=20) dissection in mastectomy patients. They also showed a significantly higher rate of seroma formation. This non-randomised study only included a small number of patients in each group. Diathermy settings were not disclosed, neither was the number of different operating surgeons mentioned. The same group published another study a few years later (Yilmaz et al., 2011) where they showed significantly higher levels of pro-inflammatory cytokines TNF-alpha and IL-6 in the drainage fluid after diathermy (n=26) dissection compared to scalpel (n=27) or ultrasonic dissection (n=29) in mastectomy patients. Study groups were again small and not randomised, and unfortunately no power calculation was performed with the data from their previous study. The major issue with this study was the collection time of the drain fluid, which was reported as within 24 hours post-operatively. As the inflammatory marker levels will raise significantly within the initial hours post-surgery (van der Heide et al., 2010), the collection time should have been narrowed down to ensure the significant difference is due to the different dissection device and not the different sample times.

Lucas et al. (2018) analysed levels of cytokines in the drain fluid of twenty autologous abdominal based breast reconstruction patients at 24-, 48-, 72- and 96-hours post-operatively. The found a significant decrease over time for cytokines IL-1, IL-2, IL-6, IL-8, IL-9, IL-10, IL-17 MIP-1 alpha, MIP-1 beta, MCP-1, IFN-gamma and TGF-alpha, stable levels for IL-7, and only an increase over time for IL-5 levels.

1.3.7 Patient factors in wound healing

Due to its complexity wound healing can be interrupted at many different levels by intrinsic and/or extrinsic factors (Table 1.3.1). Intrinsic factors are those related to the patients' overall health and further predisposing factors. Extrinsic factors are conditions affecting the patient healing capacity (Gantwerker & Hom, 2012).

Table 1.3. 1 Factors affecting wound healing (Gantwerker & Hom, 2012)

Intrinsic factors	Extrinsic factors
• Age • Immune status • Psychological stress • Hereditary healing diseases • Acquired chronic diseases	• Malnutrition • Infection • Insufficient oxygenation or perfusion • Smoking • Cancer • Radiation • Medication • Foreign material in wound • Trauma

1.3.8 Conclusion

The initial response to trauma is largely coordinated by inflammatory cytokines (Lin et al., 2000). A greater degree of tissue injury results in the production of higher levels of inflammatory cytokines (Biffl et al., 1996; Jawa et al., 2011; Stensballe et al., 2009; Taniguchi et al., 1999). The levels of inflammatory cytokines can be measured in wound fluid such as seroma fluid captured in a drain and can be compared between different operating techniques to identify the one causing the least amount of trauma (Özdogan et al., 2008; Yilmaz et al., 2011). The next chapter will explain what a seroma is, how to diagnose it and explore methods to reduce this very common donor site complication after DIEP/MS-TRAM breast reconstruction.

1.4 Seroma

A seroma is an accumulation of non-infected subcutaneous fluid (Figure 15). The name comes from *serum* (Latin for "whey") and *oma* (Latin for "tumour"), meaning "tumour from the collection of serum" suggesting it originates from the ultrafiltration of blood (P. Andrades & Prado, 2007).

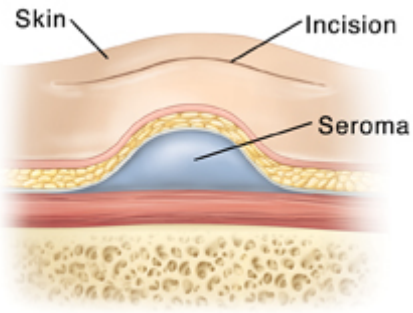


Figure 15 Collection of subcutaneous seroma fluid. Source: www.fairview.org

It is one of the most frequent donor site complications after DIEP/ MS-TRAM breast reconstruction. Reported incidence varies from 3% - 58% (P. Andrades & Prado, 2007; Kuroi et al., 2005; Miranda, Wilson, Amin, & Chana, 2015; Porter, O'Connor, Rimm, & Lopez, 1998). Di Martino et al. (2010) showed a significant increase in seroma identification (38.1%) if ultrasound is used compared to clinical examination (23.8%) because small-volume seromas can be missed clinically for example due to local oedema of the subcutaneous tissue. An ultrasound machine uses high-frequency sound waves to create images ranging from white to black with different shades of grey in between. Dense tissue like bone is white and fluids like a seroma collection are black (Figure 16).

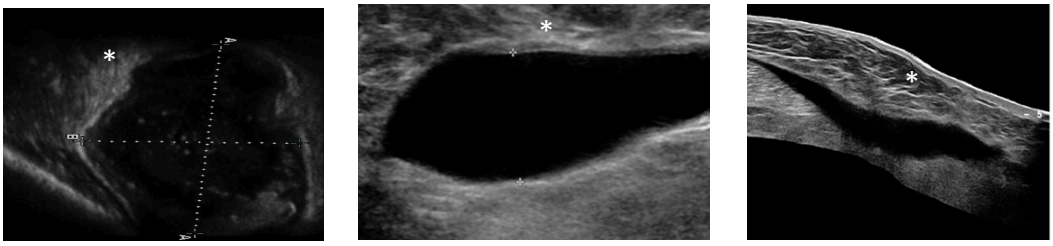


Figure 16 Seroma collections (arrow) within subcutaneous tissue (*) on ultrasound in three different patients. Source: https://www.ultrasoundpaedia.com

Formation has been positively correlated with body mass index (BMI) and flap weight (P. Andrades & Prado, 2007). A seroma can cause discomfort, wound breakdown, infection and if chronic, can turn into a pseudocyst. It is usually self-limiting, but occasionally results in significant problems requiring multiple percutaneous drainages or even surgery (P. Andrades & Prado, 2007; Kuroi et al., 2005; Porter et al., 1998).

Andrades and Prado (2007) showed post-abdominoplasty seroma is actually an exudate, which changes from an early inflammatory exudate into a late exudate with some characteristics similar to those of lymph. It's true origin is uncertain but different mechanisms have been suggested such as skills and operation technique of surgeon, creation of dead space, shear forces between skin flap and fascia, disruption of lymphatics and vessels, surgical dissection tool and the release of inflammatory cytokines following surgery (Nagarkar et al., 2016; Sforza et al., 2015; Swanson, 2015).

A prospective clinical trial published by Di Martino et al. (2015) evaluated the beginning and progression of seroma formation following abdominoplasty by performing abdominal ultrasounds at 7-day intervals in 21 female patients. Electrosurgery was used on power setting 35 Watt for cut and coagulation to carry out the abdominoplasty. Drains were removed when the output was less than 40ml/ 24 hours, resulting in a mean drain requirement of 4.4 days. Abdominal ultrasounds were performed on day 4, 11, 18, 25 and 32. They concluded the highest incidence of seroma formation was between day 11 (38.1%) and 18 (33.3%) post-operatively, which fell significantly to 19% on day 32. They also found a significantly increased incidence of seroma with an increased weight of the resected tissue.

1.4.1 Methods to reducing abdominal seroma formation

Due to the uncertain pathophysiology of seromas there is no consensus on prevention or treatment of this complication. Different methods to reduce the formation of the abdominal

seroma in both cosmetic abdominoplasties and DIEP/MS-TRAM breast reconstruction have been published over recent years (Table 1.4.1).

Table 1.4. 1 Methods to reduce abdominal seroma formation

Principle	Method
Reducing dead space	• Closed suction drains • Progressive tension or quilting sutures • Adhesives or fibrin sealants • Compression
Reducing shear forces	• The Scarpa fascia preservation • Immobilization
Reducing tissue injury	• Surgical dissection tool

1.4.1.1 Drains

Using closed suction drains help obliterate a surgically created dead space and for decades has been considered the standard of care to prevent seromas. They are usually kept in place until the output is lower than 20 to 50 ml/ 24 hours (volume subjected to surgeons' preference) (Friedland & Maffi, 2008). Considering the study results of Di Martino et al. (2015) the drains would have to stay in for a long period of time (up to 18 days) to actually capture the period of highest seroma incidence. A long indwelling drain period is usually not clinically desirable as the drain can cause pain/ discomfort, infection, limited patient mobility and potentially increase inpatient stay which result in an increased financial burden (Thacoor, Kanapathy, Torres-Grau, & Chana, 2018). In St. Andrews free flap breast reconstruction patients, drains are used and removed when producing 30 mL or less over 24 hours with a maximum of 2 weeks (see materials and methods).

1.4.1.2 Progressive tension or quilting sutures

Baroudi and Ferreira (1998) were the first to describe quilting sutures between the abdominal flap and abdominal wall fascia for cosmetic abdominoplasty surgery. Pollock and Pollock (2000), subsequently introduced progressive tension suture which not only closed the dead space but also helped to distribute tension in the abdominal skin flap as it was advanced (Figure 17).

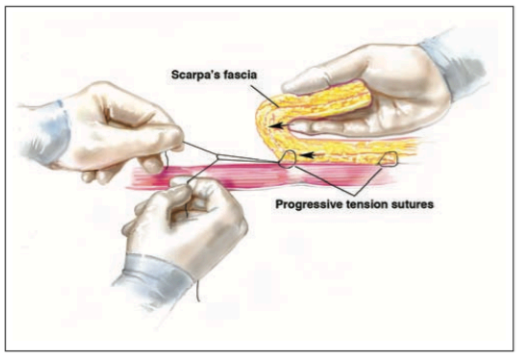


Figure 17 Progressive tension sutures closing of the dead space and distributing tension in the abdominal skin flap (T. A. Pollock & Pollock, 2012)

Multiple interrupted sutures have been criticised for introducing multiple knots which can lead to increased tissue reaction, they can cause skin dimpling and can significantly increasing length of the operating time (up to 50 min) (A. T. Mohan et al., 2015). The use of continuous absorbable barbed progression tension sutures without the use of drains has been published more recently in both aesthetic abdominoplasty and DIEP/ TRAM breast reconstruction to reduce the dead space and aid in tension free closure without significant increase of operative time (Nagarkar et al., 2016; Sforza et al., 2015; Thacoor et al., 2018).

1.4.1.3 Fibrin sealants and adhesives

Fibrin was first introduced in 1983 as a tissue sealant. It consists mainly of thrombin and fibrinogen with factor XIII derived from pooled human plasma. They function through the formation of fibrin clots, which reaches the maximal bonding strength 10 minutes after application (Mabrouk, Helal, Al Mekkawy, Mahmoud, & Abdel-Salam, 2013; Wattin & Van Loock, 2011). In theory it reduces seroma formation through three mechanisms: 1) sealing off

microvascular, lymphatic and connective tissue injuries; 2) binding tissue layers together, thereby reducing dead space and shear forces between skin flaps; 3) enabling faster revascularization of damaged tissue across suture lines (J. C. Lee, Teitelbaum, Shajan, Naram, & Chao, 2012). Different low volume trials and systemic reviews have not been able to show a statistically significant decrease in post-operative seroma after the application of fibrin sealants in abdominoplasties (Ardehali & Fiorentino, 2017; Bercial, Sabino Neto, Calil, Rossetto, & Ferreira, 2012). This could potentially be due to the large wound area and high traction forces exciding the fibrin adhesions (Gilbert, Badylak, Beckman, Clower, & Rubin, 2013; Nahas, di Martino, & Ferreira, 2012; W. Oliver, A. Hamilton, A. Figle, H. Wood, & B. Lamberty, 2002).

TissueGlu® Surgical adhesive is a synthetic, lysine-derived urethane adhesive. It is designed to adhere large tissue flaps and has been shown to be significantly more resilient to shear forces than fibrin adhesives. In a canine model the application of TissueGlu® in a surgically created pocket did reduce the seroma formation significantly up to 12 weeks post operatively (Gilbert et al., 2013). So far only two clinical trials in abdominoplasty patients have been performed, but due to poor design results are not considered valuable (Hunstad et al., 2015; Spring, 2018).

1.4.1.4 Compression - Abdominal binders

Most surgeons use some sort of abdominal support after abdominal wall surgery. This does not seem to have any significant effect on pain or seroma formation. However, subjectively the majority of patients found wearing the binder beneficial (Christoffersen, Olsen, Rosenberg, & Bisgaard, 2015). There is also no prospective study on the role of compression on established seromas, which is interesting as aspiration and compression is usually the initial treatment (Janis, Khansa, & Khansa, 2016). In St. Andrews free flap breast reconstruction patients wear an abdominal binder for 6 weeks post-operatively (see materials and methods).

1.4.1.5 Preservation of the Scarpa fascia

Scarpa fascia preservation with underlying deep fat compartment (Figure 18) was suggested by Le Louarn (1996) and has shown to reduce drain output, lead to earlier drain removal and reduces postoperative seroma formation in abdominoplasty operations. Two possible explanations for the result are: better preservation of lymphatic drainage and blood supply of the abdominal wall and better adhesion between upper skin flap and the deep fat compartment resulting in a higher resistance to shear movements (Correia-Goncalves et al., 2017; Costa-Ferreira, Marco, Vasconez, & Amarante, 2016; Costa-Ferreira, Rebelo, Silva, Vasconez, & Amarante, 2013; Koller & Hintringer, 2012; Xiao & Ye, 2017). An anatomical study showed the lymphatics are most prevalent in the superficial and deep dermis, with only approximately 17% of lymphatic vessels in the deep tissue. The clinical significance of this stays unclear but this could support the first explanation (Friedman, Coon, Kanbour-Shakir, Michaels, & Rubin, 2015).

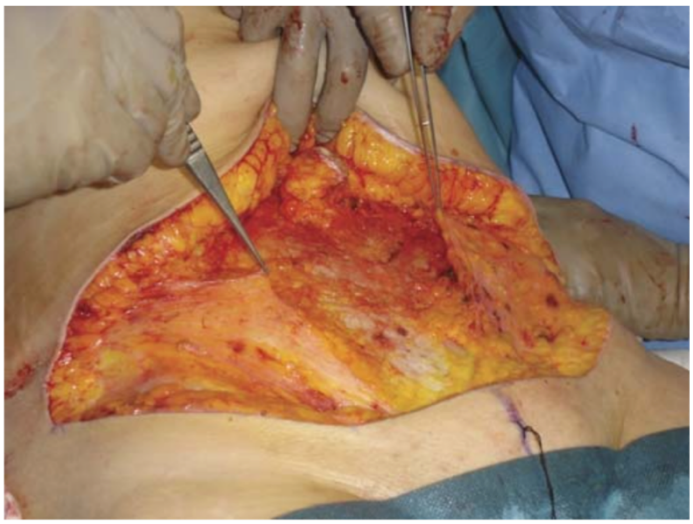


Figure 18 Preservation of the Scarpa fascia and deep fat compartment on the abdominal wall (held up by forceps) (Costa-Ferreira et al., 2016)

It must be noted that in the large RCT published by Cost-Ferreira et al. (2013, 2016) not only preservation of the Scarpa fascia but also the dissection method (electrosurgery vs blade and avulsion technique) was different between the two groups, which can also have a significant effect on seroma rates (Swanson, 2017).

1.4.1.6 Immobilisation

One study has shown to decrease the rate of post abdominoplasty seroma's by immobilising the patients up to 48 hours. Immobilisation results in a higher chance of thromboembolic complications despite prophylaxis making this method not desirable (Beer & Wallner, 2010). In St. Andrews free flap breast reconstruction patients are usually immobilised for 24hours as part of the standard post-operative protocol (see materials and methods).

1.4.1.7 Dissection tool

As described previously, electrosurgery uses electricity to achieve the clinically desired effects of separating tissue and simultaneously providing haemostasis by sealing off small blood vessels. The heat produced during electro-dissection can cause collateral tissue damage (see chapter "Electrosurgery and cautery"). Such an internal burn injury can results in an increased capillary permeability and fluid leak containing pro-inflammatory cytokines and inflammatory cells (Swanson, 2013). A greater inflammatory response with higher levels of pro-inflammatory cytokines have been shown in the seroma fluid of mastectomy patients treated with electrocautery compared to scalpel dissection (Özdogan et al., 2008; Yilmaz et al., 2011). Different studies have compared electrosurgery to scalpel dissection in abdominoplasty patients and the effect on seroma formation.

Rousseau et al. (2011) published a retrospective review comparing scalpel (n=327) dissection to diathermy (cut mode, n=320) in abdominoplasty patients. Four different surgeons in each group performed the procedures, which could be a confounding factor. Non-infectious collections, including both haematomas and seromas, were identified with an ultrasound scan, CT or needle aspiration, between day 7 and 45 post-operatively and were significantly ($p<0.05$) more common in the diathermy group (8.8%) than the scalpel group (4.9%). Patients in the diathermy group also had significantly higher average drain production and required the drain longer. The follow-up protocol was not discussed and could be a confounding factor if collection assessment was performed at different post-operative time points for the different groups. It was unclear if all patients underwent USS, CT or needle aspiration or only if there

was a clinical suspicion of a collection, which could lead to under diagnosis. Due to the retrospective character and unclarities regarding time and method of seroma diagnosis, results should be interpreted with caution.

Valença-Filipe et al. (2015) published a paper comparing scalpel (n=39) to diathermy dissection (coagulation mode, n=80) in full abdominoplasty patients. The different dissection methods were performed by one surgeon in the scalpel group and four surgeons in the diathermy group, which could be a confounding factor. This was a prospective study, without randomisation which could have resulted in selection bias. Seromas were diagnosed clinically which could result in under diagnosis and it was not reported when they were diagnosed and how long the follow-up was. Both BMI and specimen weight were significantly higher in the scalpel group, which could be confounding factors. Outcomes showed a significantly lower drain output with shorter drain requirement and hospital stay in the scalpel group. The scalpel group also experienced significantly less seromas. The findings of this study are interesting, but their value should be approached with caution due to study design which could have resulted in bias and confounding factors, for which was not corrected.

Marsh et al. (2015) published a blinded randomised controlled trial comparing scalpel (n=44) with diathermy (coagulation setting 35 Watt, n=58) dissection in abdominoplasty patients. Operations were performed by two different surgeons, but it was not clarified if the use of scalpel or diathermy was equally divided between them. A difference in experience for either of the two surgical instruments was not commented on and could be a confounding factor. No power calculation was performed. Patients were only clinically assed for seroma collections at 1-, 6-weeks and 3 months, which could result in an underdiagnosis. Seroma rates were equal between the scalpel (20.1%) and diathermy (17.2%) groups, not showing a statistically significant difference (p=0.48). Thirty-nine patients underwent liposuction in addition to their abdominoplasty. This was equally divided between the two groups but does add another variable. It was not reported if infiltration was used and at which ratio (dry, wet, super-wet or tumescent). The authors do not explain the fourteen-patient difference in group size, which is unexpected in a randomised controlled trial and could be due to patient loss to follow-up which

would be a source of bias and a possible explanation for the similar seroma rates. Despite this study supplying level 1 evidence, due to possible bias and confounding factors results should be interpreted with caution.

Swanson (2013, 2015, 2016, 2017) published one article and a few letters to editor regarding his experience with scalpel dissection in abdominoplasty reducing seroma rates. He published his 5-year cases series of abdominoplasty (n=17) and lipo-abdominoplasty (n=150) patients after super-wet infusion of up to 1L of normal saline mixed with 0.025% bupivacaine and 1:526,000 epinephrine followed by scalpel dissection and cautery for haemostasis of individual vessels. On clinical examination nine patients developed a post-operative seroma (5.4%) in the 12.26 months follow-up period, which were all treated with aspiration. Clinical assessment alone can result in an underdiagnosis of seroma presence. This large sample prospective study including patient from one surgeon presents an interesting technique possibly causing the low seroma incidence, but a future sufficiently powered RCT should supply higher level evidence. It would not be desirable to apply this infiltration technique for abdominal breast reconstruction patients as the vasoconstrictive epinephrine could complicate perforator identification.

1.4.2 Difference in seroma incidence between DIEP/ MS-TRAM and elective abdominoplasty

The elective abdominoplasty is one of the most popular aesthetic operations performed, removing excessive abdominal skin and fat tissue to improve the contouring of the abdomen (Figure 19) (Marsh et al., 2015).

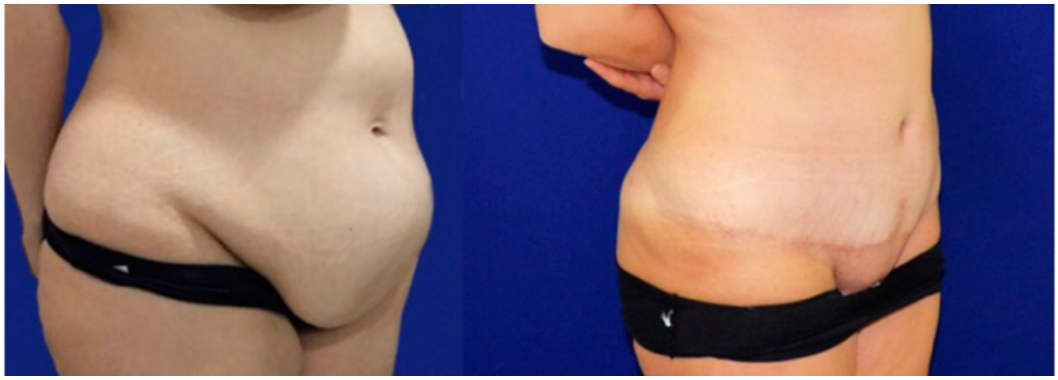


Figure 19 Elective abdominoplasty. Pre- (left) and post-operative (right) (Kurt Yazar & Serin, 2019).

Despite the identical anatomical area, publications regarding seromas in abdominoplasty patients, cannot be transferred directly to the DIEP/MS-TRAM abdominal donor site due to differences in operation technique and patient characteristics (Salgarello, Tambasco, & Farallo, 2012). Salgarello et al. (2012) published a literature review including 3,937 patients to compare short-term complication rates between DIEP flap donor site (n=1,997) and elective abdominoplasties (EA, n=1,940). They found a four-time higher incidence of seroma rates in the EA (16.1% vs 3.7%), despite intramuscular dissection and longer operating times in DIEP patients. Possible explanations given by the authors are earlier mobilisation after EA, a higher BMI in the EA cohort, the use of liposuction as an adjunct to EA, simultaneous hernia repair or rectus plication in EA and more meticulous and atraumatic dissection technique and coagulation in DIEP operations.

1.4.3 Conclusion

A seroma is an accumulation of non-infected subcutaneous fluid of uncertain origin. Its occurrences is reported between 3 and 58% after DIEP/MS-TRAM breast reconstruction (P. Andrades & Prado, 2007), with the highest incidence between day 11 and 18 (M. Di Martino et al., 2015). Methods to reduce dead space, shear forces and/ or tissue injury have been published to reduce or eliminate seroma formation.

In St. Andrews suction drains, compression garment and 24-hour immobilization are part of the normal protocol after abdominally based breast reconstruction. In the search of methods to reduce drain requirement and seromas formation in the DIEP/MS-TRAM patient population, publications on the subject were evaluated on evidence and applicability: 1) Progressive tension or quilting sutures could add operating time to an already long free-flap breast reconstruction and was therefore less appealing; 2) Currently the use of fibrin sealants and adhesives in large wounds lacks evidence on its ability to reduce seroma formation; 3) Preservation of the Scarpa fascia would not be possible in a DIEP/MS-TRAM breast reconstruction procedure as this would make identification, isolation and preservation of the perforator very difficult; 4) Reduction of the effects of electrosurgery was the most promising method to reduce drain requirement and seroma formation and was also the easiest to implement. Therefore, the next chapter will explain the principle of electrosurgery, possible side effects and explore alternative modalities trying to overcome these.

1.5 Electrosurgery and cautery

In prehistoric times, heated stones were used for cautery. Ancient Egyptian writings describe the use of heated tips to produce tissue coagulation (Jones, Pierre, Nicoud, Stain, & Melvin, 2006). The use of electricity in medicine started at the end of the 18th Century. In 1897, Franz Nagelschmidt introduced the term diathermy (Massarweh, Cosgriff, & Slakey, 2006). This comes from the Greek words 'through heat', to describe the heating effect caused by a current passing through the body (Boyd & MacG Palmer, 2013; Massarweh et al., 2006).

The first use of electricity in surgery was in 1900 by Joseph Riviere who utilised an arching current from an electrode to treat a carcinomatous ulcer on a patient's hand (Massarweh et al., 2006). Around 1910 William Clark made further advancements to the electrosurgical apparatus by increasing the amperage and decreasing the voltage which resulted in a hotter and shorter spark that could penetrate deeper into the tissue (Massarweh et al., 2006).

In the early 1920s biophysicist Dr William T Bovie of Harvard University developed the first version of the instrument we use today. He constructed a diathermy unit producing high-frequency current delivered through a loop which could be used for coagulation, cutting and desiccation (tissue destruction by dehydration) (Jones et al., 2006; Massarweh et al., 2006). Dr Harvey Cushing, neurosurgery director in Boston was the first to use this machine in October 1926 to remove an enlarged vascular myeloma. He had attempted removal of the mass several days earlier but was unsuccessful due to the vascularity of the tumour (Massarweh et al., 2006). The Liebel-Flarsheim Co purchased the patent from Bovie for only 1 dollar and started the production of the unit for other operating theatres (Jones et al., 2006; Massarweh et al., 2006).

1.5.1 Conventional radiofrequency diathermy

Electrosurgery is described as high-frequency electrical current creating a clinically desired effect while passing through tissue. This is different from electrocautery where an electrical current heats an instrument and application of heated tool to the tissue causes the clinical effect (Messenger, Carter, & Francis, 2014; Sankaranarayanan, Resapu, Jones, Schwaitzberg, & De, 2013). Electrons follow Ohm's Law (Table 1.5.1) when passing through an electrical circuit (Jones et al., 2006).

Table 1.5. 1 Ohm's Law

Voltage = Current x Resistance

Voltage (V):	Force driving a current against the resistance of the circuit (in Volts)
Current (I):	Flow of electrons during given period (in Amperes, Amps)
Resistance (R):	Difficulty to pass an electronic current through tissue dependent on water content (in Ohms)

In electrosurgery the voltage is created by a generator and an electrode tip of the instrument delivers the current to the human tissue, which has got an inherent resistance. Electrons will always seek the path of least resistance. If the circuit is incomplete the current will seek the ground, which can cause burns in patients (Massarweh et al., 2006; Messenger et al., 2014).

Electrical energy is transformed into heat (in Watts or Joules) according to Joules Law (Table 1.5.2).

Table 1.5. 2 Joules Law

Energy (Heat) = (current/cross-sectional area) x (Resistance x Time)

< 45°C: Reversible thermal damage to tissue
> 45°C: Proteins denaturalize and loss off structural integrity resulting in coagulation
> 90°C: Evaporation of liquid in tissue resulting in desiccation or vaporization
> 200 °C: Fulguration or carbonization where solid tissue components reduce to carbon

Due to the small surface area of the active electrode a concentrated heating effect is produced at the point of contact with the patient's tissue (Figure 20) (Jones et al., 2006; Messenger et al., 2014).

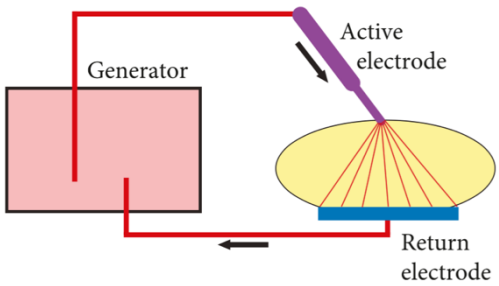


Figure 20 An electrosurgery circuit. High current density at the active electrode generates heat when passing through tissue (Arash Taheri et al., 2014).

An alternating current (AC) changes its direction of flow, in contrary to a direct current (DC) which does not change direction. The rate of change is called frequency, measured in Hertz (Hz, cycles per second) (Hay, 2008; Jones et al., 2006). It was discovered by Morton in 1881 that an alternating current with frequency of 100 kHz could pass through the human body without causing spasm, pain or burns. Direct or low frequency (<100 kHz) alternating currents cannot be used as they can activate susceptible tissues resulting in neuromuscular stimulation, muscle contraction, cell membrane depolarisation and even cardiac arrhythmias (Massarweh et al., 2006; Arash Taheri et al., 2014; A. Taheri et al., 2014). Electrosurgery uses high-frequency alternating currents around 500 kHz to achieve the heating effect without killing or injuring (electrocuting) the patient. (Gallagher, Dhinsa, & Miles, 2011; Hay, 2008; Arash Taheri et al., 2014).

Electrosurgical generators can modulate the current output (mode) resulting in the delivery of different waveforms with different effects on the tissue (Table 1.5.3).

Table 1.5. 3 Modes of energy delivery

- Cut mode: continuous sinusoidal waveform
- Coagulation mode: interrupted sinusoidal waveform
- Blend: modification to the degree of current interruptions

The output voltage can be adjusted to deliver the same amount of power in the continuous and interrupted modes (Gallagher et al., 2011). In the coagulation mode, current exposure to the tissue is interrupted and only 6% of the activation time (Figure 21). This allows more thermal spread within the tissues, which reduces production of heat and results in a slower rise of tissue temperature leading to a coagulum. The cut mode on the other hand results in a fast rise in temperature causing rapid expansion of the intracellular contents and explosive vaporization. This leads to a fine tissue incision with minimal coagulation (Gallagher et al., 2011).

Besides the output modes and power settings, a number of other factors like size and geometry of the electrode delivering the energy, exposure time and manipulation of the electrode influence the depth and the rate at which heat is being produced and its effect on the tissue (Massarweh et al., 2006).

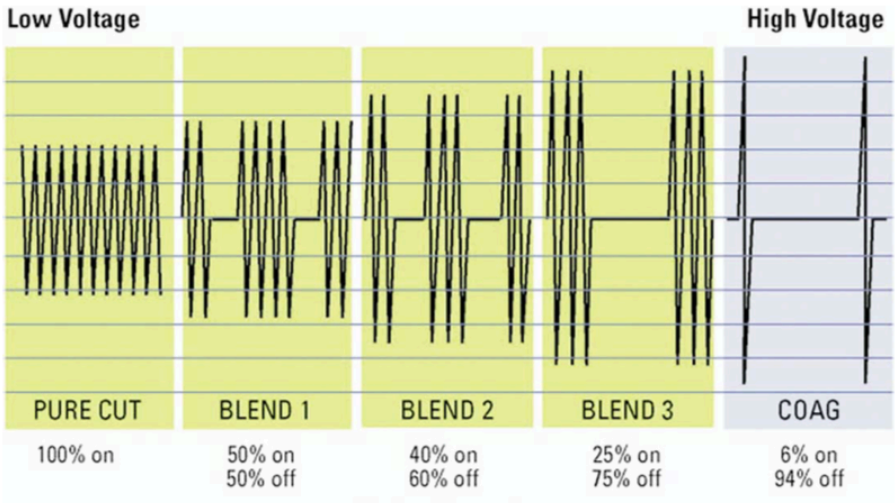


Figure 21 Relation of instrument settings to voltage and current interruption (Massarweh et al., 2006)

Manipulation of the electrode is one of the most important factors in achieving the wanted surgical effect. By holding the electrode in the cut mode in close proximity to the tissue allows arcing which results in vaporization of intracellular content, dividing the tissue. Arcing in the coagulation mode causes a coagulum over a larger area due to higher voltage waveforms. Direct contact with the active electrode causes the tissue to dry out and form a coagulum (desiccation). Cutting can be achieved in both the coagulation and cut mode, with the latter requiring less voltage due to the continuous current. A higher voltage generates a greater force on the electrons in a circuit which can lead to increased or uncontrolled thermal spread (Figure 22) (Arash Taheri et al., 2014).

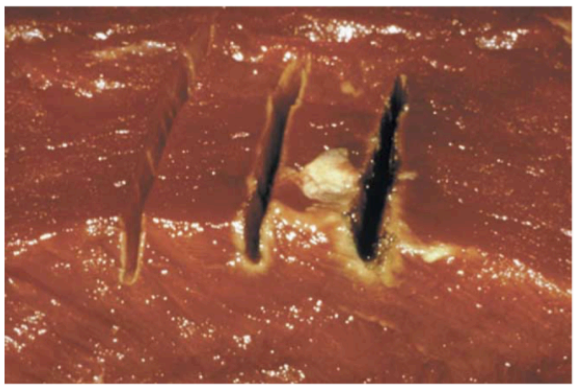


Figure 22 Thermal spread at different generator settings (Massarweh et al., 2006)

Generators can provide energy in a monopolar or bipolar fashion (Figure 23). With the monopolar a dispersive electrode pad is required to complete the circuit by passing the current from the body back into the generator (Figure 24a). The much larger surface area of the return electrode facilitates dissipation of the current returning to the generator, which minimizes local heat production.

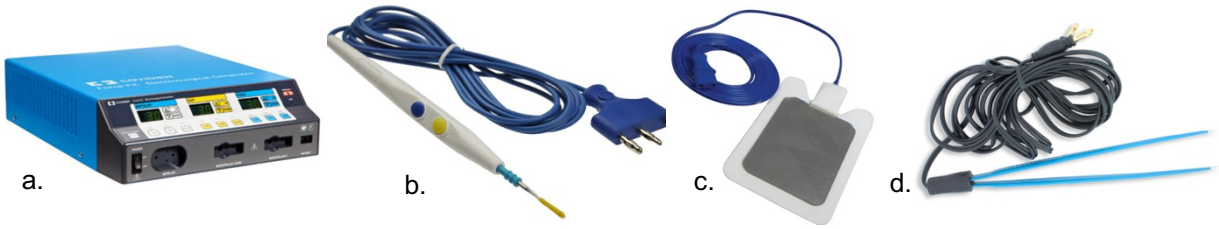


Figure 23 Electrosurgery: a. Generator; b. Monopolar diathermy; c. Dispersive electrode pad; d. Bipolar

Bipolar delivery is without a dispersive return electrode pad as the patient's body is not part of the circuit (Figure 24b). The target tissue grasped between tips of the forceps completes the circuit. A much lower voltage can be used, which results in very small chance of unintended dispersal of current (Messenger et al., 2014). Today's generators use closed-loop control loops so the voltage and current can be adjusted when the monopolar moves through tissues of varying resistance, leading to a constant output power (Massarweh et al., 2006).

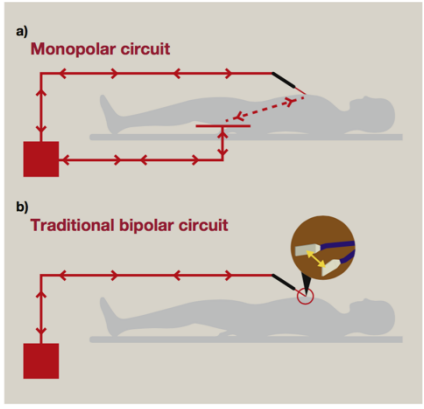


Figure 24 Electro circuits a. Monopolar circuit; b. Bipolar circuit (Messenger et al., 2014)

The published incidence of intra-operative electrosurgical injuries from the 1970s through the 1990s has been 2 to 5 per 1,000 and is often operator dependent (Massarweh et al., 2006). In all circumstances, a higher voltage carries a greater risk of perioperative complications (Table 1.5.4, Figure 25) (Boyd & MacG Palmer, 2013; Gallagher et al., 2011; Hay, 2008; Jones et al., 2006; Sankaranarayanan et al., 2013).

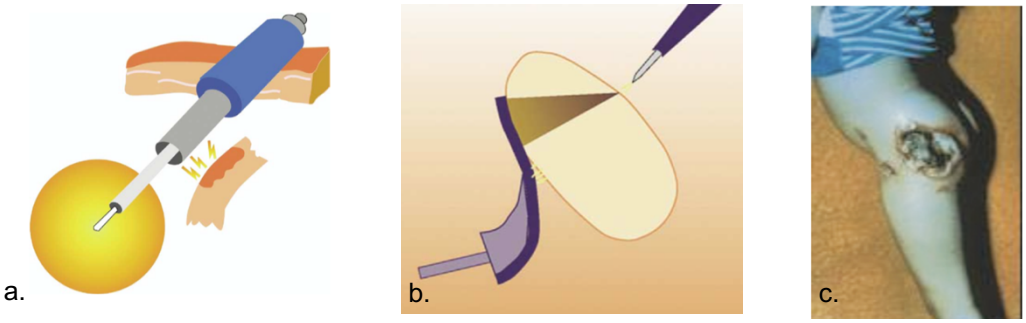


Figure 25 a. Capacitive coupling; b. Inadequately applied grounding pad; c. Large off-side burn on left buttocks due to poorly adherent grounding pad (Jones et al., 2006; Massarweh et al., 2006).

Table 1.5. 4 Possible perioperative electrosurgical complications

- Inadvertently activation
- Interference with pacemakers or implantable cardioversion devices
- Current concentrations in the tips of the lead wires
- Conductive joint within circuit
- Insulation failure
- Direct coupling and capacitive coupling (Figure 25a)
- Off-site burns due to improper grounding (Figure 25b and 25c)
- Fire and explosion
- Surgical smoke inhalation
- Complications to surgeon

1.5.2 Models to describe thermal injury to the skin and subcutaneous layers

Thermal injury to cells depends on the temperature height and exposure time. The critical temperature, also called the "break point", a human cell can withstand is around 43.5 $^{\circ}$C, above this, irreversible alterations in proteins lead to cellular death (Ye & De, 2017). An Arrhenius analysis can be used to determine the heat required to inactivate cells, by plotting the rate of cell killing ($1/D_0$; D_0 = number of minutes to reduce survival by 63%) vs 1/temperature ($^{\circ}$K) (Figure 20). Formula to calculate heat of inactivation:

$$K = Ae^{(-\frac{E}{RT})}$$

E = heat of inactivation in kcal/mole, A = is a constant over the temperature range studied, R = molar gas constant (1.987 x 10^{-3} Kcal/mole-$^{\circ}$K) and T = absolute temperature in $^{\circ}$K (Dewhirst, Viglianti, Lora-Michiels, Hanson, & Hoopes, 2003).

Arrhenius plots (Figure 26) are typically biphasic around the "break point', with the slope being steeper below the break, related to the occurrence of thermos-tolerance of the tissues. Above the break for every degree temperature increases, cell killings double (Dewhirst et al., 2003).

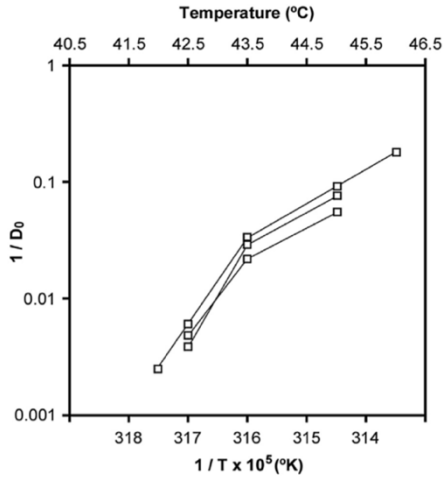


Figure 26 An Arrhenius plot displaying the relationship between a kinetic constant ($1/D_0$) and the inverse temperature, with a 'breakpoint' at 43.5 ˚C (Martin & Falder, 2017).

Sapareto and Dewey introduced a formula to convert a time-temperature combination to an equivalent number of minutes at 43˚C. This is termed 'thermal iso-effective dose' and used in hyperthermia treatment:

$$CEM43\ ºC = tR^{(43-T)}$$

CEM 43 ˚C = cumulative number of equivalent minutes at 43 ˚C, t = time (minutes), T = average temperature during time interval t. R = number of minutes needed to compensate for a 1 ˚C temperature change either above or below the breakpoint (threshold temperature for damage) (Dewhirst et al., 2003).

One well defined time-temperature combination can be extrapolated, but might not be accurate at temperatures below 39 ˚C or above 57 ˚C, possibly due to non-linearity's in the surface and deeper layer skin temperature relationship and heat transfer (Dewhirst et al., 2003). A partial or complete reduction in bloods supply to a region of the body increases the thermal sensitivity of the tissue, making it more susceptible to thermal injury (Dewhirst et al., 2003).

A second formula to quantify cell injury caused by thermal exposure is the damage or thermal injury index Ω, which is more commonly used in thermal ablation practice. It gives the ratio

between the pre-treatment number of undamaged cells C(0) to the remaining number of undamaged cells after time τ , indicated by *C(τ).*

$$\text{Damage index} = \Omega(\tau) = ln\left\{\frac{C(0)}{C(\tau)}\right\} = \int_0^{\tau} Ae^{\left[-\frac{E_a}{RT(t)}\right]dt}$$

A = frequency factor (1/s); E_a = activation energy (J/mol); R = universal gas constant (8.3143 J/mol-K); T = temperature in Kelvin and t = time (Viglianti, Dewhirst, Abraham, Gorman, & Sparrow, 2014).

The longest time a constant surface temperature can be endured without resulting in irreversible trans-epidermal necrosis was established at Ω = 0.53. With Ω = 1 being the shortest time resulting in complete trans-epidermal necrosis (Martin & Falder, 2017).

Due to its thinness, the epidermis does not contribute significantly to the response after a thermal injury (Ye & De, 2017). As collagen is one of the main components of the skin, it is assumed to be one of the main proteins affected by thermal damage (Viglianti et al., 2014). Owing to the tissue's inherent resistance (impedance) applied electricity will be converted into heat. Permittivity of skin (ϵ_{skin}=1832.8) is much higher than fat (ϵ_{fat}=27.22), therefore skin polarises much easier than fat making it less resistive to an electric flux. Electric conductivity for skin (σ_{skin}=0.22) is also much larger than that of fat (σ_{fat}=0.025) (Jimenez-Lozano, Vacas-Jacques, Anderson, & Franco, 2012).

Subcutaneous tissue is made up by a fine fibrous and collagenous septa network, surrounding clusters of adipocyte fat cells. Current passing through fat and septa form different electric environments. As electric conductivity of the septa is one magnitude larger than the conductivity of fat in subcutaneous tissue, it is more favourable for electric currents. Therefore, the intensity of the electric field is larger in fat, due to higher resistivity. There is great variety in density and orientation of the fibrous septa networks between individuals, resulting in

different electric fields and distribution of thermal response within the subcutaneous tissue (Gonzalez-Suarez, Gutierrez-Herrera, Berjano, Jimenez Lozano, & Franco, 2015).

1.5.3 Concerns regarding electrosurgery

The use of electrosurgery causing collateral heat damage has raised concerns regarding poor wound healing and increased infection rates resulting in excessive scaring. The support for these concerns came from different experimental studies in rats which showed significantly more extensive tissue necrosis and inflammatory response in abdominal fascia incisions with diathermy compared to cold scalpel with a reduced tensile strength (S. G. Kumagai et al., 1991; Ozgun et al., 2007; Rappaport et al., 1990). Soballe et al. (1998) published a study with the misleading title “Electric cautery lowers the contamination threshold for infection in laparotomies”. They performed an experimental study including 375 rats where fascia incisions with either scalpel, diathermy cut setting (30 Watt) or diathermy coagulation (30 Watt) was performed followed by bacterial inoculation (different levels of bacteria: 0, 10^3, 10^5, 10^7, or 10^9). Histological specimens showed significantly more inflammation and necrosis in the diathermy coagulation group at all levels of bacterial inoculation, compared to the diathermy cut and scalpel group. Comparison between the diathermy cut setting and scalpel only showed a significant difference in inflammation and necrosis at level 10^5 bacteria, above that threshold most wounds were infected in all three groups. The National Institute for Health and Clinical Excellence (NICE) recommended in the 2008 published guidelines against the use of electrosurgery for skin incisions due to increased concerns regarding surgical site infection (Leaper et al., 2008). Subsequent large randomised clinical trials comparing scalpel and electrosurgery for abdominal incisions included in two published Cochrane systemic review (16 RCTs, 2769 participants) (Charoenkwan, Chotirosniramit, & Rerkasem, 2012; Charoenkwan, Iheozor-Ejiofor, Rerkasem, & Matovinovic, 2017) contradicted this recommendation as no significant differences in wound infections or wound dehiscence were found, but further research is needed to draw a firm conclusion as evidence was low with a significant risk of bias.

Ismail et al. (2017) did not find a significant difference in wound characteristics in their systemic review of nine heterogeneous studies, including 2720 participants between cutting diathermy and scalpel, neither did they find significant differences in objective scar assessment at 120 days in two studies including 171 participants or subjective scar assessments in two studies including 185 participants.

Most clinical studies suggest electrosurgical incision of skin significantly reduces bleeding and operating time compared to the use of scalpel (AbdElaal, Ellakwa, Elhalaby, Shaheen, & Aish, 2019; Kearns, Connolly, McNally, McNamara, & Deasy, 2001; Talpur, Khaskheli, Kella, & Jamal, 2015). This was also reported by a meta-analysis by Ly at al. (2012) including 14 RCTs with a total of 2541 patients and by Ismail et al. (2017) in their systemic review and meta-analysis including 41 studies with a total of 6422 patients. The studies included in the Cochrane systematic review (Charoenkwan et al., 2017), did not find a significant difference in blood loss (3 RCTs, 241 patients) or incision time (4 RCTs, 325 patients) between the diathermy and scalpel.

1.5.4 Alternative modalities

Over the years, different novel energy-based surgical technologies have been introduced, trying to overcome the potential negative effects of electrosurgery (Table 1.5.5).

Table 1.5. 5 Different energy-based surgical technologies (MacDonald, Bowers, Chin, & Burns, 2014; Sankaranarayanan et al., 2013)

	Instrument	Modality	Positives	Negatives
Conventional Electrosurgery	-"Bovie" Monopolar - Bipolar	Electricity	- Cheap - Efficient haemostasis	- Thermal injuries - Surgical smoke - Can interfere with implanted medical devices
Ultrasonic energy	- Harmonic scalpel	Mechanical vibrations	- Lower temperature with minimal thermal spread - No smoke production	- Learning curve - Not as efficient for sealing medium to large blood vessels - Slower coagulation
Laser		Light	- Extremely accurate - Decreased postoperative discomfort	- Higher costs - Need for advanced training - Eye protection - Risk of fire - Less accessible - Increased operative time - Generation of air embolisms
Argon beam coagulation		Argon gas conduction of radio frequency current	- Faster, uniform and shallower coagulation - Minimal Tissue damage due to low temperature - Less smoke	- Gas embolisms which can be fatal
Ferromagnetic induction	FMwand®	Alternating magnetic field	- Lower temperature, reducing lateral thermal damage - No electrical current through patient - Precise	- Expensive
Radio frequency energy	PEAK PlasmaBlade™	Electricity	- Lower temperature - No blade for skin incision required	- Expensive

1.5.4.1 Ultrasonic energy

Ultrasonic energy was first used in medicine in 1960 for the treatment of Ménière's disease (Sankaranarayanan et al., 2013). In the late 1980s ultrasonic dissection was popularised in laparoscopic surgery to avoid monopolar associated risks, like thermal injuries (Sankaranarayanan et al., 2013). Electrical energy from a generator gets converted by the ultrasonic device into ultra-high frequency mechanical energy (55.5 kHz or vibrations/second). The generated heat seals blood vessels up to 5 mm in diameter by causing protein denaturation and coagulum formation (Messenger et al., 2014). Studies have shown that ultrasonic devices are not as efficient in sealing medium to large sized blood vessels (Sankaranarayanan et al., 2013). Heat generated with ultrasonic dissection does not exceed 150 °C which minimizes the distance of thermal spread leading to minimal thermal tissue injury (Chilaka Obonna & Mishra, 2014; Messenger et al., 2014; Sankaranarayanan et al., 2013).

1.5.4.2 LASER (Light Amplification by Stimulated Emission of Radiation)

Lasers were first used in 1979 in laparoscopic surgery but have gained widespread popularity in different medical field such as cosmetic and dermatological treatments, atrial fibrillation treatments and gynaecological procedures (Sankaranarayanan et al., 2013). Laser generate heat by a concentrated beam of light. The high intensity light waves are formed in a laser system which amplifies electromagnetic or light waves multiple fold in an optical resonator. The light waves transmit energy when they get absorbed by tissue, leading to heat which cuts and coagulates (Sankaranarayanan et al., 2013). The power of a laser is measured in terms of 'irradiation' is defined as the ratio of power applied to the spot-size of the laser beam (W/m^2). Time of exposure and wave length (frequency) are two other variables that need to be considered when using lasers in surgery (Sankaranarayanan et al., 2013). Disadvantages are higher cost of specialised equipment, the need for advanced training and eye protection, risk of fire and it is less accessible than electrosurgery (Sankaranarayanan et al., 2013; Arash Taheri et al., 2014).

1.5.4.3 Argon beam coagulation (ABC)

The first use of argon beam coagulation was reported by Ward and colleagues (1989). From the electrode tip a beam of argon gas helps to conduct radiofrequency current to the tissue by ionization. This results in a non-contact method where the argon gas transports the current to the tissue (Messenger et al., 2014; Sankaranarayanan et al., 2013). ABC is faster and more precise than conventional coagulation, provides a shallower and more uniform coagulation area, leading to faster dispersion and therefore minimizing tissue damage. This also prevents tissue carbonization and gives a clearer field of vision by reducing smoke production (Hay, 2008; Sankaranarayanan et al., 2013). The greatest risk of ABC systems is the argon gas embolism, which can be fatal. To reduce this risk a low argon flow rate should be used, direct contact of the tip with the tissue should be avoided and the tip should be held in an oblique angle (Sankaranarayanan et al., 2013).

1.5.4.4 Ferromagnetic induction (FMI)

A 4- to 10 µm thick coating of ferromagnetic alloy on a tungsten loop tip creates heat through a rapidly alternating magnetic field generated by a high frequency electrical current, which is sufficient enough to incise and seal tissue. No grounding pad is required (MacDonald et al., 2014). This technique results in a lower tissue temperature (75 °C) at the margin of the incisions leading to a thermal injury depth of only 10 to 25% of that associated with standard monopolar electrosurgery (MacDonald et al., 2014; Starr, Gates, Palafox, & Quill, 2016).

1.5.4.5 Radio frequency (RF) energy

Radio frequency is a type of electromagnetic radiation, which ranges from 3 kHz to 300 MHz. Due to its low frequency RF takes longer to generate heat in tissue (Sankaranarayanan et al., 2013).

The pulsed-electron avalanche knife (PEAK) PlasmaBlade™ device uses this technology. Due to the relevance of this device to the research described in this thesis, the following section will describe its features in more detail.

1.5.5 PEAK PlasmaBlade™ (PPB) device

The PEAK PlasmaBlade™ device (Medtronic Advanced Energy, LLC., Portsmouth, New Hampshire, Figure 27) uses very brief pulses (40 μsec) of radio frequency energy to create electrical plasma along the edge of a thin (12.5 μm) 99.5% insulated electrode. This creates a cutting edge with simultaneous haemostatic properties.

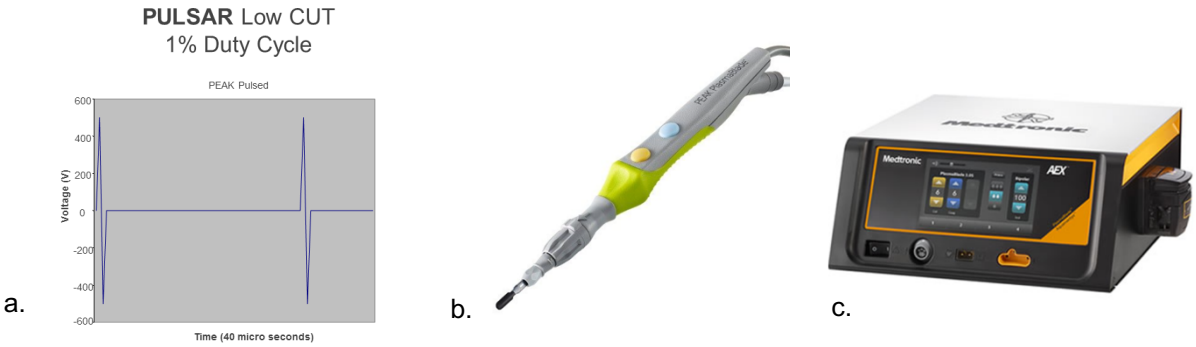


Figure 27 a. Duty cycle of 1% in cut mode; b. PEAK PlasmaBlade™ hand piece; c. PEAK PlasmaBlade™ generator. Source: Medtronic.com

Plasma is an electrically conductive cloud comprised of water vapour and charged ions from the breakdown of tissue (Loh et al., 2009). With a burst rate of less than 1 kHz and a duty cycle not exceeding 5% in cut mode, this technology uses less total energy and operates at significantly lower temperatures than traditional electrosurgical devices (40 °C -170 °C vs 200 °C - 350 °C), which leads to less depth of lateral thermal damage (LTD) (Loh et al., 2009). Ughratdar et al. (2018) also showed the PEAK PlasmaBlade™ used in the cut mode (setting 4 - 5) significantly reduced intraoperative smoke formation compared to traditional electrosurgery (1.8 vs. 38.7 mg average mass of smoke particulate) in neuromodulation implant revision.

The machine is CE-marked and cleared by the US Food and Drug Administration. Traditional electrosurgery devices are significantly cheaper (£20 vs £200) (Fine & Vose, 2011). Table 1.5.6 shows different characteristics of both the conventional diathermy and PEAK PlasmaBlade™.

Table 1.5. 6 Characteristics of the conventional diathermy and the PEAK PlasmaBlade™

	Conventional Diathermy	**PEAK PlasmaBlade™**
Introduced in (year)	1920s	2008
Type of electromagnetic radiation	High frequency energy	Low radiofrequency energy
Frequency (kHz)	500 kHz	1 kHz
Cut cycle duty (%)	100%	Less than 5%
Mode	Continuous alternating	Pulses
Operating temperature (°C)	200 - 350 °C	40 - 170 °C
Costs (£)	20	200

1.5.5.1 Experimental studies comparing incisions created with the PEAK PlasmaBlade™ to electrosurgery and scalpel.

Experimental studies have shown skin incisions with the PEAK PlasmaBlade™ used in the cut mode have a wound-healing profile comparable to that of scalpel incisions and superior to those of conventional electrosurgical incisions with respect to inflammation, wound strength and thermal zone of necrosis (Chang, Carlson, Vose, Huang, & Yang, 2011; Ekin et al., 2018; Loh et al., 2009; MacDonald et al., 2014; Ruidiaz et al., 2011). In this paragraph the published experimental studies will be presented in the order of publication date.

The first paper comparing healing of surgical incisions created with a scalpel, conventional diathermy and the PEAK PlasmaBlade™ was in a porcine skin model, published by Loh et al. (2009). Parameters examined were instrument operating temperature, blood loss, inflammation, histologic coagulation necrosis, wound cosmesis/ scarring and wound tensile strength.

On six Yucatan swine 3 cm full-thickness incisions were made on day 0, 21, 28, 35 and 42 using a no. 10 scalpel, the PEAK PlasmaBlade™ on cut setting 3 (6 Watt) and a conventional diathermy on cut (40 Watt, Blend 2) and coagulation (40 Watt, Spray). Instrument operating temperatures were captured with a Thermavision SC600 infrared camera while moving the instrument approximately 0.5 to 1cm/sec. The PPB reached an average temperature of 45 °C compared to the much higher temperatures of the diathermy of 241 °C in cut and 180 °C in the coagulation mode (Figure 28).

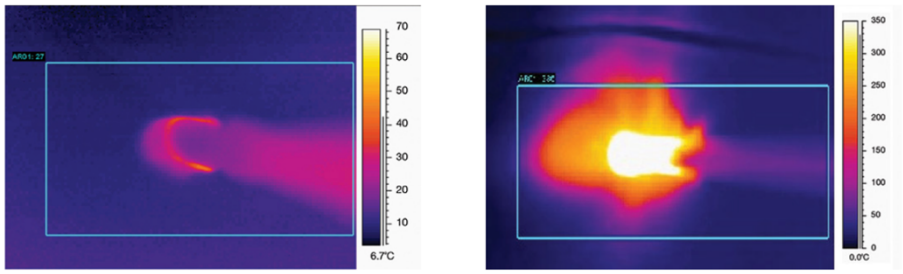


Figure 28 Infrared images of operating temperature profiles of the PEAK PlasmaBlade™ (left) and conventional diathermy (right) (Loh et al., 2009)

Blood loss was evaluated with filter paper-based bleeding analysis (relative area unit = 10^5 pixels) measuring 2.50 ± 0.32 for the scalpel, 1.03 ± 0.27 for the PPB, 0.52 ± 0.33 for electrosurgical cut and 0.29 ± 0.29 for electrosurgical coagulation mode. The difference between the scalpel and PPB was significant (p=0.002), this was not shown for the PPB and electrosurgery modes (p=0.23 and p=0.07).

Inflammation was examined under high-power magnification (40x) by counting number of T lymphocytes ($CD3^+$), macrophages ($CD68^+$) and myofibroblasts by a blinded observer. By week 3, the PPB incisions contain significantly less T lymphocytes. The number of macrophages was highest in the 1-week specimens, with the lowest amount seen in the PPB incision. At six weeks the electrosurgical coagulation setting had significantly more macrophages than the other modalities. The scalpel and PPB incisions showed similarly low levels of myofibroblasts, compared to significantly higher prevalence for both electrosurgical modes throughout the entire 6-week time period. The lower levels of these cells suggest less

inflammation is induced after the use of the PPB compared to the conventional electrosurgical cut and coagulation settings.

Formalin fixed, haematoxylin and eosin stained specimens were evaluated by light microscopy by a single pathologist in a blinded manner. The zone of thermal coagulation necrosis was significantly ($p<0.0001$) narrower in PPB incisions (66 ± 5 µm) compared to electrosurgical cut (456 ± 35 µm) or coagulation mode (615 ± 22 µm) (Figure 29).

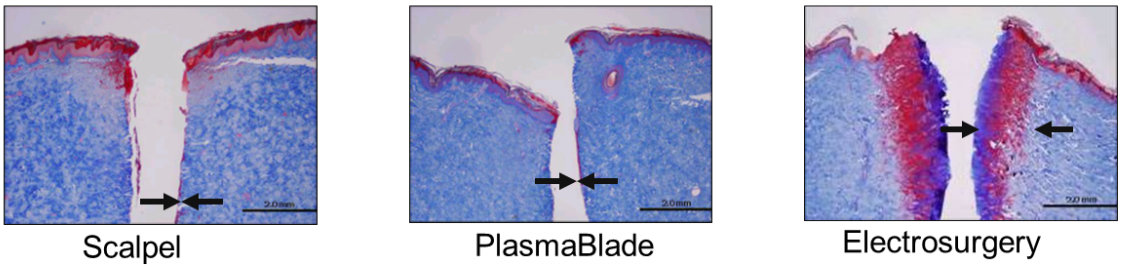


Figure 29 Different widths of zone of thermal necrosis (Loh et al., 2009)

Scar width was comparable between the scalpel and PBB. Both were significantly narrower than the electrosurgical scars and showed superior aesthetic outcomes.

To test the wound strength the incision line was aligned in clamps and a progressive force (extension rate of two inches per minute) was applied until the scar disruption. The scalpel and PPB incisions showed greater burst strength compared to electro-surgical incisions at every time point.

In this study 30 wounds were evaluated for each instrument, created at five different time points. Optimal power settings were determined by extensive pilot studies. The average instrument operating temperatures were not measured while performing this study, but on tissue at room temperature. It was not reported how many measurements were performed or after how long this temperature was reached and if it was the maximum temperature possible or if it was the maximum temperature reached within the time of the incision. The significantly smaller zone of thermal necrosis, reduction in inflammatory markers and increased wound burst strength after the use of the PEAK PlasmaBlade™ compared to electrosurgery could

indicate less inflammation due to reduced collateral tissue damage which resulted in improved wound healing and significantly narrower scars after six weeks, which is a short scar follow-up time. The significant results in this pig study provide evidence to support the hypothesis that the use of the PEAK PlasmaBlade™ could reduce collateral tissue injury in breast reconstruction patients and improve recovery.

The second experimental study published by Chang et al. (2011) compared healing of 90 rat fascia's following incision with three surgical instruments, traditional "cold" scalpel (SC), conventional electrosurgery (CE – cut 40 Watt, Blend 2 and coagulation 40 Watt, Spray modes) and PEAK PlasmaBlade™ (PPB - cut setting 3 (6 Watt)). Harvested fascia specimens were examined on burst strength, depth of thermal injury and histologic healing-associated scores on day 7, 14, 21 and 42.

Burst strength was determined by slow progressive stressing of a segment till disruption at a speed of 2 inch /min. This only showed a significant difference ($p = 0.001$) between the 1-week specimens of the EC-coag vs the PPB, with all four surgical methods regaining equivalent burst strength of uncut fascia at the end of 6 weeks.

On histological samples the zone of tissue injury was significantly larger in both coagulation (68% greater $p<0.0001$) and cut (46% greater $p<0.0001$) EC-modes and surprisingly for incision by SC (25% $p=0.024$) compared to the PPB.

In this study five fascial wounds were evaluated for each instrument at four different time points. Results of burst strength were compared to a control group. Used settings were chosen based on a previous pilot study. Histopathologic characters we scored by a blinded single pathologist, but the objective rating of this and the healing scores makes it less reliable values. Difference were given in percentages and p values only for comparison with the scalpel incision. A decreased zone of tissue injury, which appears to be evaluated at all different time points, after PPB incision even compared to scalpel incision was speculated to be caused by decreased inflammation. This evaluation of zone of tissue injury does not reflect the thermal and/ or mechanical injury correctly and can only be done shortly after infliction to

prevent introduction of other forms of bias such as the inflammatory response. Due to the critiqued study outcomes and evaluation this study was less valuable.

The third paper comparing the healing of human cutaneous incisions created by PEAK PlasmaBlade™, Conventional diathermy and scalpel was published by Ruidiaz et al. (2011). In 20 healthy female adult subjects undergoing an abdominoplasty, three 5cm full-thickness skin incisions were made with a no. 10 scalpel, PPB on Cut setting 3 (6 Watt) and conventional diathermy in cut mode (30 Watt) at 6- and 3-weeks pre-operative and immediately before the abdominoplasty (Figure 30).

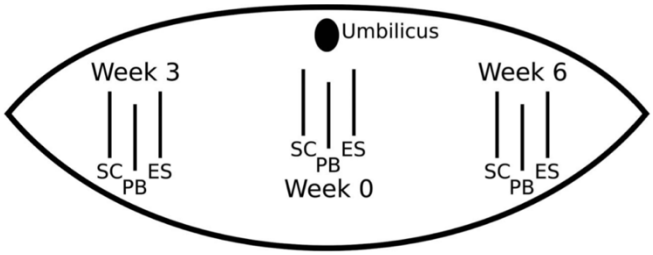


Figure 30 Arrangement of incisions made by scalpel (SC), PlasmaBlade (PB) and electrosurgery (ES) at 6- and 3-week pre-operatively and immediately before abdominoplasty (week 0) (Ruidiaz et al., 2011)

Thermal injury depth was significantly lower in the PPB samples, compared to the conventional diathermy ($p<0.001$). Burst strength of the PPB scars was equivalent to the scalpel scars and was significantly better than conventional electrosurgery ($p<0.001$). Only the 3-week PPB scar was significantly narrower than the electrosurgery scar ($p=0.01$). Inflammatory markers $CD3^+$ and $CD68^+$ were significantly higher after the use of the conventional diathermy compared to scalpel and PPB for the 3-week scars.

In this study 60 human wounds were evaluated for each instrument at three different time points. In agreement with the previous studies in porcine skin and rat fascia, it was found that the PPB resulted in lower thermal injury depth and an increased burst strength, compared to the conventional electrosurgery. This was the first experimental study in humans in a novel cutaneous wound healing model. Long-term scars evaluation was not performed and the significant difference in scar burst strength might have disappeared beyond the 6-week follow-

up period. The significant results in this human model also provide evidence to support the hypothesis that the use of the PEAK PlasmaBlade™ could reduce collateral tissue injury in breast reconstruction patients and improve recovery.

The last experimental study published on the subject by MacDonald et al. (2014) compared incisions created in rabbit livers using monopolar electrocautery (MPE, settings 40/40 Watt Blend2), harmonic scalpel (HS, settings 3 - 5), PEAK PlasmaBlade™ (PPB, settings 9 - 1) and ferromagnetic induction loop device (FMI, settings 60 Watt). In three rabbits, three incisions were created with each of the four instruments (12 incisions in each liver) by a single surgeon. Subjective coagulation and cutting qualities (tissue drag, haemostasis, margin uniformity and collateral tissue damage) were scored (1= optimal, 5 = unsatisfactory) for each device. The subjective scoring did show some significant differences mainly between the PPB vs MPE and FMI vs MPE.

Histological analysis of the tissue specimens for lateral thermal damage was performed by a single pathologist, resulting in a damage index ratio (damaged tissue area divided by the incisional depth). This revealed a comparable damage index for incisions created with the PPB, FMI and HS. The damage index was significantly higher for the incisions created by MPE.

In this study nine rabbit liver incisions were evaluated for the four different instruments, incision for the usual baseline values with a scalpel was not performed. It was not specified if the PPB was used in the cut or coagulation setting and the 9-1 cannot be identified on the settings chart (appendix 1). Device settings used were not tested in a pilot study. The pathologist analysing the histological samples was not blinded which could introduce bias. The value of significant findings for the subjective scoring of characteristics of the surgical dissection is questionable due to its subjective character. Due to the unclear used settings for the PEAK PlasmaBlade™ these study results were less valuable.

1.5.6 Conclusion

Since its introduction in the early 1900s, electrosurgery has become an important tool in surgical practice (Ly et al., 2012) as it enables surgeons to cut and perform haemostasis simultaneously. Experimental studies in animals raised the concern electrosurgery could lead to poor wound healing and an increased risk of complications such as surgical site infection, however clinical trials do not seem to support this (Charoenkwan et al., 2012; Charoenkwan et al., 2017; Ismail et al., 2017; Ly et al., 2012). The PEAK PlasmaBlade™ is a new electrosurgical device that can operate on a lower temperature due to brief pulses of radiofrequency energy (Loh et al., 2009). Experimental studies in animal and human models comparing skin incisions with scalpel, electrosurgery (cut and coagulation mode) and the PEAK PlasmaBlade™ have shown wound profiles with less inflammation, a higher burst strength and a smaller zone of thermal necrosis for the PEAK PlasmaBlade™ compared to conventional electrosurgery (Loh et al., 2009; Ruidiaz et al., 2011). These findings make the PEAK PlasmaBlade™ an interesting alternative to the conventional diathermy. In DIEP/MS-TRAM breast reconstruction patients a lower operating temperature could cause less collateral thermal damage which would reflect in lower pro-inflammatory cytokine concentrations and possibly less drain fluid production and complications such as seroma formation. The next chapter will present the conducted literature review on clinical studies comparing the PEAK PlasmaBlade™ to conventional diathermy for tissue dissection.

1.6 Literature review: Clinical studies comparing PEAK PlasmaBlade™ to conventional electrosurgery

For this part of the introduction a literature search was conducted including all papers published on PubMed comparing the PEAK PlasmaBlade™ to conventional diathermy for tissue dissection in clinical studies. Search terms used were “PEAK PlasmaBlade”, “PlasmaBlade”, “Plasmakinetic Cautery” and “Plasma Surgery”. References of included papers were also reviewed for relevant publications. The search was limited to the English and German language. Clinical studies where only skin was incised or use for simple excision (tonsillectomy and wound debridement) were excluded. The search resulted in the inclusion of eight papers, which are chronologically presented by publication date. Each study will be briefly summarised and study design, outcomes, flaws and inconsistencies will be discussed. Tables 1.6.1 and 1.6.2 give an overview of the included papers.

Table 1.6. 1 Summary eight clinical studies included

First author, Year publication	Study design	Number of included patients and procedure	Compared machines	Outcome measures
Ruidiaz , 2011	RCT	20 abdominoplasties (CE n=10, PPB n=10)	CE vs PPB	- Operating time - Course of healing - Drainage duration
Dogan, 2013	Prospective case study	46 mastectomies (CE n=22, PPB n=24)	CE vs PPB	- Operation time - Intra-OP blood loss - Drainage amount - Drainage duration - Start arm exercises - Complications
Chiappa, 2018	Prospective experimental study	60 breast cancer surgery (CE n=40, PPB n=20)	CE vs PPB	- Operating time - Intra-OP blood loss - Drainage duration - Hospital stay - Complications
Zientara, 2018	Prospective experimental study	20 bilateral internal thoracic artery harvest (CE n=20, PPB n=20)	CE vs PPB	- Operating time - Histological assessment distal part ITA harvest - CT for patency

Sowa, 2018	Retrospective cohort study	44 LD breast reconstructions (CE n=22, PPB n=22)	CE vs PPB	- Operating time - Drainage amount - Drainage duration - Hospital stay - Seroma rates
Kypta, 2018	Retrospective cohort study with propensity score matching	762 cardiac device replacements (CE n=508 vs PPB n=254)	CE vs PPB	- Operating time - Hospital stay - Complications - Lead damage - Cost analysis
Schlosshauer, 2019	Retrospective study	9 upper arm lifts and 15 thigh lifts	CE vs PPB	- Drainage amount - Drainage duration - Histological acute thermal injury depth
Duscher, 2019	Four-armed, open-label randomised trial	57 abdominoplasties (CE n=14; PPB n=12; UHS n=14; APC n=17)	CE vs PPB vs UHS vs APC	- Operating time - Intra-OP blood loss - Drainage amount - Complications
CE = conventional electrosurgery, PPB = PEAK PlasmaBlade™, ITA = Internal thoracic artery, UHS = Ultracision harmonic scalpel, APC = Argon Plasma Coagulation				

Table 1.6. 2 – Clinical studies included: Main findings, strengths and limitations

First author	Main findings	Strengths	Limitations
Ruidiaz	- No difference in operating time (p=0.47) - No difference in drain duration - No difference in course of healing	- RCT	- Very limited information regarding RCT protocol and results - RCT never published
Dogan	- No difference in operating time - No difference in the amount of blood loss - Significantly less drainage PPB group (p=0.025) - Significantly shorter drainage duration PPB (p=0.020) - No difference in start arm exercises - No difference in complications	- Prospective study - Equal baseline characteristics groups	- Small sample size - No randomisation - No blinding - Wide range energy setting both machines - Number different surgeons not mentioned neither experience level - Only collection requiring multiple drainages considered as seroma - No information on follow-up regime

Chiappa	- No difference in operating time (p=0.737) - No difference intra-OP blood loss (p=0.095) - No difference in drainage amount (p=0.761) - No difference in mean draining duration (p=0.061) - No difference in hospital stay (p=0.509) - Significant difference between seroma incidence (p=0.034) - No difference other complications	- Equal baseline characteristics groups	- Small patient population - Power settings not disclosed - Number different surgeons not mentioned neither experience level - Limited information on seroma
Zientara	- Significant quicker harvest CE (p=0.001) - Significantly less endothelial damage (p=0.04) - No difference in vessel integrity and adventitial haemorrhage - No significant difference in patency ITA on CT scan	- Comparing different machines in one patient - Equal random distribution of sides harvested by different devices - One operating surgeon - Standardised settings machines - One pathologist blinded to machine type to evaluate specimens	- Modification preparation technique during study due to insufficient bleeding control in PBB group - Only distal ITA harvest evaluated - Novel scoring system for vessel evaluation
Sowa	- No difference in operating time (p=0.98) - Significantly shorter hospital stay (p<0.011) - Significantly less Drainage (p=0.0358) - No difference drain requirement (p=0.16) - Lower seroma incidence (p<0.043)	- Equal baseline characteristics groups	- Retrospective study - Small sample size - Potential confounders not considered - Number different surgeons not mentioned neither experience level - Power settings not disclosed
Kypta	- Significantly shorter operating time (p<0.001) - Significantly shorter hospital stay (p<0.0001) - Significantly less lead damage (p<0.001). no difference in infection or haematoma. - Over-all per patient saving of €81 in PPB patients	- Propensity score matching for baseline characteristics - Three experienced surgeons - Objective outcomes	- Retrospective - Possible time trend bias as machines never used side-by-side

Schlosshauer	- No difference in 1st post-op drainage day (p=0.106) - Significant difference in drainage volume (p=0.041) - No difference in drainage duration (p=0.109) - No difference in thermal injury depth	- Comparing two different machines on the same patient - Histological specimens reviewed by one pathologist - Standardised machine settings - Clear follow-up protocol	- Baseline characteristics two groups unknown - Some patients also receiving liposuction which can be a confounding factor - Wide range of electrosurgery settings were used - Number different surgeons not mentioned neither experience level - Side distribution not disclosed - Seroma not defined nor method of diagnosis
Duscher	- No difference in wound healing - No difference in operating time - No difference in drainage volume - No difference in complications such as haematoma and seroma	- Allocation randomised - All operations by one surgeon and two residents - Clear study protocol - Standardised settings different machines	- Open label - Small numbers - Baseline characteristics different groups unknown - For drainage amount only range all groups - Five patients excluded for incomplete FU
CE = conventional electrosurgery, PPB = PEAK PlasmaBlade™, ITA = Internal thoracic artery, FU = Follow-up			

Ruidiaz et al. (2011) published a paper mainly focussing on comparing cutaneous wound healing, inflammatory response and thermal injury depth after skin incisions with a scalpel, conventional electrosurgery and the PEAK PlasmaBlade™ in 20 women undergoing an abdominoplasty. In the methods it is stated the data were collected as part of a randomised controlled trial of 20 adult female subjects undergoing abdominoplasty with either the PBB™ or scalpel and conventional electrosurgery. Mean operating time between the two different machines for the abdominoplasty was not significant (1h 39 min vs 1h 35 min p=0.47). There is limited information on the outcome of this RCT, with only mentioned in the results “the clinical course of healing and time to drain removal was comparable between the two groups”. It was not clarified which settings were used for either the PEAK PlasmaBlade™ or the conventional diathermy, neither was reported what the drain removal protocol was. It is

unknown why the results of this PEAK PlasmaBlade vs. traditional Electrosurgery in abdominoplasty (PRECISE) study were never published.

Dogan et al. (2013) published a prospective study including 46 consecutive patients undergoing modified radical mastectomy, randomly allocated to either have their operation performed with the PEAK PlasmaBlade™ (n=24) or conventional electrocautery (n=22). Electrocautery was used in both cut and coagulation modes between 20 to 30 Volt and the PPB was used in both cut and coagulation modes between settings 6 to 8. Drains were used and removed when draining 50mL or less over 24 hours. A statistically significant difference between drain output (707 vs 1,093mL, p=0.025) and drainage duration (5.5 vs 7.9 days, p=0.020) in mastectomies favouring the use of the PEAK PlasmaBlade™ over conventional electrocautery. Operation duration, intra-operative blood loss, time to start arm exercises and complications such as seroma, haematoma, infection and mastectomy skin flap necrosis didn't not differ significantly.

This prospective study without randomisation or blinding only included a small number of patients in each group. The authors describe the use of the plasmakinetic cautery device on the numeric settings between 6 to 8 in both coagulation and cutting mode which corresponds to a power between 20 - 50 Watt. This wide range is potentially higher than the 20 - 30 Watt (the paper mentioned Volt, but this is most likely an error) used for the electrocautery, this makes us question if the difference in drainage amount and duration is solely based on the two different machines. Possibly, variations in the amount of lymphatic leak after axillary dissection in the respectively 27.2% and 29% of the patients in each group, could have had an influence on the amount and duration of drainage. No comment was made regarding the number of different operating surgeons. The published lower median total drainage volume in the plasma cautery group does not mean less seroma fluid was produced as the initial blood loss in the immediate post-operative period can contribute significantly to the total drainage volume. As a definition of seroma, the paper used "clinically diagnosed fluid collection under skin flap or axilla requiring multiple aspirations". This means any fluid collection not requiring

or only requiring one drainage would not be regarded as a seroma, which results in an under estimation of this complication.

Chiappa et al. (2018) published a single-institution observational study including sixty patients undergoing breast cancer surgery (40% mastectomy and 60% quadrantectomy). Twenty patients who had their operation performed with the PEAK PlasmaBlade™ were matched to 40 conventional diathermy cases, based on age, BMI, co-morbidities and procedure type. They did not find a significant difference in mean drainage duration (PPB 14.31 ± 5.23 vs 10.93 ± 5.17 in control group, p=0.06), nor in the daily amount of drainage (PPB 60.15 ± 28.23 vs 56.78 ± 34.53 in the control group, p=0.761). Also, surgical duration, intra-operative blood loss and length of hospital stay were equal. Seroma incidence between the two groups did significantly differ in favour of the PlasmaBlade™ group (PPB 10% vs 37.5% in the control group, p=0.034). Other complications such as haematoma, infection and skin flap necrosis did not differ significantly.

This study only involved a small patient population of 20 operated with the PPB. The paper did not disclose the used power settings for either of the machines and if they were standardised, neither was commented on the number of different surgeons performing the procedure and their experience level. A significant difference in seroma incidence was diagnosed, but method of diagnosis (clinical or USS), size, time of detection and requirement for intervention were not reported. The flaws in study design make it impossible to correlate significant or non-significant finding to the use of either of the two machines as they could very well be caused by other confounding factors. For the statistical analysis normal distribution of the data was not analysed.

Zientara et al. (2018) published a prospective experimental study comparing the PEAK PlasmaBlade™ to conventional electrosurgery for the harvest of skeletonised internal thoracic artery (ITA). The study included twenty subjects undergoing coronary artery bypass grafting with both internal thoracic arteries. In each patient one artery was prepared with the PEAK

PlasmaBlade™ and the other with a conventional electrosurgery device. All procedures were performed by a single surgeon. PEAK PlasmaBlade™ settings were coagulation-5 (equal to 35 Watt) and cut-1 and for the conventional electrosurgery device the coagulation setting was 20 Watt. Machine side for harvest was randomly allocated before the start of the procedure and resulted in a balanced distribution of 10 right and 10 left ITAs harvested by each device, resulting in a total of 40 grafts. Time to complete the harvest was recorded individually for each machine. At the epigastric bifurcation a 5 cm arterial sample was taken for histological analysis of endothelial damage (scored as percentage of circumference damage 0 = 0%, 1 = 1 – 25%, 2 = 26 – 50%, 3 = 51 -75% and 4 = over 75%), integrity of vessel wall and adventitial haemorrhage by a single pathologist. Patency of the bypass graft was evaluated at 6 months by cardiac computed tomography.

Histological analysis showed a statistically significant reduction in endothelial damage in samples harvested with the PPB (83% vs. 60% samples with a score of “0-1”, p=0.04). There was a trend towards better wall integrity, but this was not statistically significant. The was no difference in the presence of adventitial haemorrhage. Harvest time with the PPB was significantly longer for the PPB (26.3 min vs. 21.2 min, p=0.001). It was mentioned the surrounding tissue bed after harvest with the PPB required additional coagulation by the conventional electrosurgery device and resulted in a modification of the preparation technique, clipping both proximal and distal ends of side branches. It was unclear if this modification was introduced for both conventional diathermy and PPB group and at which stage during the study the modification was initiated. On CT scan all fifteen ITAs prepared with conventional diathermy were patent, one of the ITAs harvested with the PBB was occluded.

The main flaw of the study is the difference of preparation technique which was introduced while conducting the trial. If vessel clips were used more often in the PPB group due to problems with haemostasis, this could be a major confounding factor and the reason for the significant difference in endothelial damage. Another limitation of the study is the use of the distal end for histological analysis, which might not be representative for full length of the artery.

Sowa et al. (2018) published a retrospective study including 44 patients undergoing LD breast reconstruction surgery. Patients in the PPB group had a significantly lower total drain discharge (883.8 vs 624.4, p=0.0358) and required a significantly shorter hospital admission (14.1 vs 11.7 days, p=0.011). There was no difference between operating time, intra-operative blood loss or drain requirement between the two groups. The incidence of seromas was significantly higher in the electrocautery groups (47.8% vs 19%, p=0.043).

This retrospective study used medical notes to obtain information of the two small patient groups. There was no comment on missing data, used settings of the PPB and conventional monopolar or the number of different operating surgeons, which makes it difficult to comment on the results. A seroma was defined as a persistent fluid collection for more than 4 weeks. According to this definition fluid collections requiring multiple puncture drainages but resolving within 4 weeks would not be considered a seroma, resulting in an under estimation of this complication. This definition of seroma has never been encountered in any other publication and raises the suspicion it was introduced to create a significant difference in seroma occurrence between the two groups.

Kypta et al. (2018) published a retrospective cohort study including 762 patients from two centres who underwent an electrosurgical generator replacement of an implantable cardiac device with either scissor, scalpel and electrosurgery or the PEAK PlasmaBlade™. Due to the low thermal stability of the material covering the leads the use of electrocautery can cause severe damage resulting in their malfunction. Propensity score matching was applied to create two groups with similar age and gender, resulting in 508 patients in the conventional group and 254 in the PPB group. The procedure was performed by one of three experienced operators. The PPB group showed a significantly lower incidence of lead damage (5.3 vs 0.4%, p<0.001) and both operating time (47.9 vs 34.1 minutes p<0.001) and hospital stay (3.2 vs 2.4 days, p<0.001) were significantly shorter as well. A cost analysis based on the cost of

consumables, duration of operating time and the cost due to complications was performed and showed a potential over-all per patient saving of €81 when the PPB was used.

Study limitations were the retrospective character and possible time trend bias as the conventional strategy was stopped after implementation of the PEAK PlasmaBlade™. The reviewed period of 13 years will also have had an effect on surgeon experience, which could contribute to the difference in incidence of lead damage and operating time. The significant difference in hospital stay might not only be explained by the difference in operating machine but also by changes to local hospital health policies between 2003 and 2015.

Schlosshauer et al. (2019) published a retrospective study including 24 patients undergoing upper arm or medial thigh lifts. Each patient served as their own control with random allocation of the PEAK PlasmaBlade™ to one side and the monopolar electrosurgery to the other. The electrosurgery device was used at cut setting: auto; dry cut: effect 4, max. 180 Watt; forced coag: Effect 2, max. 80 Watt. The PEAK PlasmaBlade™ cut setting was used between 5 – 6 and coagulation at 7. Twenty specimens were histologically evaluated for acute thermal injury depth by a single pathologist blinded to which machine was used. The total drain output on the PEAK PlasmaBlade™ side was significantly lower compared to the conventional monopolar side (61.1 vs 95.1 mL, p=0.04). No difference in day one drain output, time till drain removal or complications such as seromas, haematoma and wound healing problems was observed. No difference in thermal injury depth was found in the ten microscopy specimens from the two different machines. This retrospective study only included a small patient population. Each patient was consent before undergoing the procedure, therefore the presentation of this study as retrospective seems incorrect. Five patients underwent simultaneous liposuction (with unknown infiltration technique), which has been published to increase post-operative drainage (Salgarello et al., 2012). The used settings for the monopolar were very high, with a maximum coagulation setting of 80 Watt and cut of 180 Watt. The PEAK PlasmaBlade™ settings were significantly lower with cut 5-6 (20 Watt) and coagulation 7 (35 Watt). Surprisingly, analysis of 20 specimens did not show a significant difference in thermal damage depth between the two groups. In the results three major complications requiring reoperation were reported for the

PPB group, but Table 2 only displays two major complications. It seems unlikely the two haematomas in the PEAK PlasmaBlade™ group were included into the total drain and day 1 drain volume as this would have significantly increased both values. Only the total operating time was reported, it would have been more valuable to measure time for each side separately. No comment was made on the number of different surgeons performing the procedure and their experience level with either of the machines, neither was reported if the side distribution of each machine was equal as surgeons' hand dominance usually makes one side easier to perform. No definition of seroma or method of diagnosis (clinical or USS) was given, neither was the length of follow-up mentioned. Two of the "Key messages" outlined are untrue as the PPB did not show as statistically significant difference in tissue damage neither did it result in a statistically significant reduction in postoperative seromas. This paper quotes results of the PEAK PlasmaBlade vs. traditional electrosurgery in abdominoplasty (PRECISE) study as showing a markedly diminished serous drainage (31% less drainage p=0.02) and less morbidity in the PPB group despite this never being published.

Duscher et al. (2019) published a randomised open label study comparing four different surgical devices for abdominoplasty dissection in 57 patients. All procedures were performed by one senior surgeon and two residents. Used settings for the electrocautery (n=14) were 60 Watt – cut blend, 40 Watt – coagulate spray; for the Ultracision Harmonic scalpel (n=14) stage 5; for the PEAK PlasmaBlade™ (n=12) setting 3; and the Argon Plasma Coagulation (APC, n=17) at 80 Watt with a Plasma surgery Flow of 2.0 L/min. Blood loss was evaluated by weighing gauzes. Abdominal drains were inserted and removed when producing 30 mL or less over 24 hours. Compression garments were used for 8 weeks post-operatively. Patients were seen in the out-patient clinic weekly for the first two weeks, followed by a 3-month and 1-year appointment. Clinical suspicion of seroma was verified with USS and drained if painful. There was no significant difference in operating time between the four operating machines, neither did the total drainage differ significantly. The Ultracision method resulted in a significant increase in blood loss (100.2 mL, $p < 0.01$), compared to the other methods. No

significant differences in complications such as seroma, haematoma and wound healing problems were experienced. A cost analysis was performed based on personal costs, surgical device costs and surgical time. Ultracision and the PEAK PlasmaBlade™ were associated with higher costs compared to the APC and electrocautery, without showing any clinical benefit. The open label character of the study could be a cause of bias in this small group randomised trial. Five patients were excluded from the study because they had not attended all the follow-up appointments. This decision will have led to exclusion bias and an intention-to-treat analysis would have been more valuable. It was not disclosed if there were any significant differences in the baseline characteristics of the groups, as only the average age, BMI and pre-operative weight loss were mention for the whole group. Neither were the exact value given for the total drainage amount for each group.

The Canadian agency for drugs and technologies in health (CADTH) publish a rapid response report in August 2019 where they attempted to review clinical effectiveness and cost-effectiveness of the pulsed electron avalanche knife (PEAK) PlasmaBlade™ versus traditional electrocautery for surgery (Peprah & Spry, 2019). From a total of 49 citations identified in their literature research, eight articles (Table 1.6.3 - three RCTs and five retrospective cohort studies) were included into the review.

Table 1.6. 3 Papers included in clinical effectiveness and cost-effectiveness of the PEAK PlasmaBlade™ (Peprah & Spry, 2019)

Author, Year, Publication country	**Study design**	**Population characteristics**	**Compared modalities**	**Clinical outcomes**
Duscher et al., 2019, Austria	Single-centre, four armed, open-label randomised trial	57 abdominoplasty patients 2014 - 2016	PPB, EC, UHS and APC	- Procedure times - Intraoperative blood loss - Drainage quantity - Wound complications

Tan et al. 2019 Singapore	Single-centre prospective double-blinded RCT	58 tonsillectomy patients 2013 - 2014	PPB vs monopolar EC	- Post-OP pain - Complications - Pain-killer tablets - Days till normal diet - Days till normal activity - Days till pain-free swallowing - Patients satisfaction
Marangi et al. 2018 Italy	Single-centre prospective, single-blinded RCT	45 chronic ulcer patients 2012 - 2016	PPB vs EC	- Thermal and mechanical damage at incision site - Inflammatory response - Granulation tissue/ collagen deposition - Incidence of post-operative infection - Healing time
Kypta et al., 2018 Austria	Retrospective cohort study on patient data from two hospitals	762 patients undergoing surgical implant replacement 2003 - 2015	PPB vs EC	- Time procedure - Hospital stay - Complications - Lead damage
Sowa et al., 2018 Japan	Retrospective cohort study using medical charts	44 LD breast reconstruction patients	PPB vs EC	- Time procedure - Hospital stay - Seroma - Post-OP bleeding - Drainage indwelling time - Drainage volume
Lane et al., 2016 USA	Retrospective cohort study using chart analysis	1780 tonsillectomy patients 2011 - 2013	PPB, monopolar EC and coblation	- Post-OP bleeding - Hospital admissions - ED visits
Kypta et al., 2015 Austria	Retrospective cohort study from registry data	611 patients undergoing surgical implant replacement 2003 - 2014	PPB vs. EC	- Time procedure - Hospital stay - Complications - Lead damage
Thottam et al., 2015 USA	Retrospective cohort study using chart analysis	1280 paediatric adenotonsillectomy patients 2011 - 2013	PPB, monopolar EC and RF-ablation	- Time procedure - Post-OP bleeding
PPB = PEAK PlasmaBlade™, EC = Electrocautery, UHS = Ultracision Harmonic Scalpel, APC = Argon Plasma Coagulation, RF = Radiofrequency, RCT = Randomised Controlled Trial, LD = Latissimus dorsi, ED = Emergency Department				

Unfortunately, all papers reviewed were of low quality with design flaws introducing a high chance of bias. The data suggest operating with the PEAK PlamsaBlade™ resulted in significantly shorter wound healing time (Duscher et al., 2019), shorter post-OP hospital stay (Kypta et al., 2018; Kypta et al., 2015; Sowa et al., 2018), earlier pain free swallowing (Tan et al., 2019), shorter drain requirement (Sowa et al., 2018), higher patient satisfaction (Tan et

al., 2019), less damage to device leads (Kypta et al., 2018; Kypta et al., 2015) and less incision site thermal damage (Marangi et al., 2018) compared to conventional electrocautery. No significant differences were observed regarding post-op bleeding (Lane, Dworkin-Valenti, Chiodo, & Haupert, 2016), post-op haematomas (Kypta et al., 2018; Kypta et al., 2015) and inflammatory response (Marangi et al., 2018). Inconsistent evidence was found regarding length of procedure (Kypta et al., 2018; Kypta et al., 2015; Thottam et al., 2015), drainage volume (Duscher et al., 2019; Sowa et al., 2018), post-op seroma (Duscher et al., 2019; Sowa et al., 2018) and post-op infection rates (Kypta et al., 2018; Kypta et al., 2015; Marangi et al., 2018) with some finding significant results in favour of the PEAK PlamsaBlade™ and others with no differences between the PPB and conventional electrocautery. Reported inconsistent results between some of the studies could be due to the variety of surgical procedures at different anatomical sites. The conclusion was: "there is insufficient evidence to conclude on the clinical effectiveness of the PEAK PlasmaBlade™ compared with electrocautery for surgery", neither was there relevant evidence regarding the cost-effectiveness of PPB for surgery identified (Peprah & Spry, 2019).

Conclusion

At the beginning of this randomised controlled trial only the papers by Ruidiaz et al. (2011) and Dogan et al. (2013) were published. Over the recent years more studies have been published comparing the PEAK PlasmaBlade™ to conventional diathermy. Unfortunately, as concluded by the Canadian agency for drugs and technologies in health, papers reviewed were of low quality with design flaws introducing a high chance of bias. Commonest flaws or weaknesses were: small sample sizes without power calculation; poor study design; wide range of or non-disclosed energy settings of electrosurgical machines; non-disclosed or high number of different operating surgeons; different definitions of seroma; only clinical assessment of seroma collections; unclear follow-up protocol.

A well-designed, sufficiently powered study comparing the PEAK PlasmaBlade™ to conventional diathermy for tissue dissection was therefore required to supply a higher level of evidence regarding differences in clinical outcomes between both machines. The conducted double blinded randomised controlled trial has aimed to meet all these criteria and will be presented in the rest of the thesis.

1.7 Hypothesis

Breast cancer is one of the commonest forms of cancer in the UK with around 62,000 newly diagnosed cases every year. Of this group 25-30% will have to undergo a mastectomy leading to significant asymmetry. In 2002, the National Institute for Health and Clinical Excellence (NICE) recommended that "*reconstruction should be available [to all women with breast cancer] at the initial surgical operation*." Autologous reconstruction usually provides the best cosmetic and durable result but requires additional scars to the donor area and a longer operating time, hospital stay and recovery compared to implant-based reconstruction.

The initial response to trauma, such as surgery is largely coordinated by endogenous soluble mediators referred to as inflammatory cytokines. They are produced by systemic immune cells and other cell types at the site of injury. A higher degree of tissue injury results in production of higher levels of pro-inflammatory cytokines, which can be measured in wound fluid. Levels of most cytokines are highest 24 hours after the injury.

Seroma is one of the most common donor site complications after DIEP or MS-TRAM breast reconstruction. Due to the uncertain pathophysiology there is no consensus on how to reduce its occurrence. Avoidance of electrosurgery in abdominoplasties has shown promising results in reducing seroma formation but cannot be transferred directly to the DIEP/MS-TRAM abdominal donor sites and should therefore be further explored for this patient group.

Electrosurgery uses an electrical current to cut through tissue. This device has increased the surgical possibilities due to ability to cut and simultaneously coagulate blood vessels. One of the downsides of electrosurgery is the collateral thermal damage to the surrounding tissue. Over recent years new technologies have been introduced trying to reduce this. One of these devices is the PEAK PlasmaBlade™ which can operate on a lower temperature due to very brief pulses of radiofrequency energy. Different experimental studies in both animal and human models comparing the PEAK PlasmaBlade™ and other surgical dissection devices for

incisions have shown a reduction in width of zone of thermal injury, reduction in wound inflammation, increased wound strength and reduced scaring in favour of the PEAK PlasmaBlade™ and comparable to scalpel incisions. A prospective clinical study published by Dogan et al. in 2013, including 46 consecutive breast cancer patients receiving a modified radical mastectomy either with the conventional diathermy (n=22) or the PEAK PlasmaBlade™ (n=24), showed a statistically significant reduction in wound fluid production (p=0.025), leading to earlier drain removal (p=0.020) in the PEAK PlasmaBlade™ group.

The flap raise in abdominal based autologous breast reconstruction (DIEP/ MS-TRAM) with the aid of electrosurgery, results in a large wound surface. Comparable to oncological breast surgery (mastectomy), prolonged drain requirements for high wound fluid production and seromas are often experienced in the post-operative course. To evaluate the effects of the PEAK PlasmaBlade™ for abdominal dissection in autologous breast reconstruction on wound fluid production and complications such a seroma, this double blinded randomised controlled clinical trial was conducted.

This is the first large double blinded randomised controlled clinical trial comparing the PEAK PlasmaBlade™ to the conventional diathermy in DIEP/ MS-TRAM flap harvest. This study differs from previous studies as it includes a large population of breast reconstruction patients (n=108) which is sufficiently powered to identify a one-day difference in drain requirement, based on data from a previously conducted pilot study. This study also included the collection and testing of drain fluid samples to enable comparison of inflammatory cytokine profiles between the two groups. Complications were recorded and to reliably identify seroma collections an abdominal ultrasound was performed at the 2- and 6-week follow-up appointments.

I hypothesised that the use of the PEAK PlasmaBlade™ for the DIEP/ MS-TRAM flap harvest would result in 1) a reduced abdominal drains time requirement; 2) a lower total drainage from

the abdominal drains; 3) lower levels of inflammatory cytokines in the drain fluid and 4) less seroma and smaller seromas development in the follow-up period.

1.8 Study aim and objectives

The aim of the study was to evaluate if there is a difference in outcomes after the use of the PEAK PlasmaBlade™ for the raise of the DIEP/ MS-TRAM flaps, compared to the conventional diathermy.

- The primary outcome value compared between the two groups was:
  - o Number of days the abdominal drains were required
- Secondary outcome values compared between the two groups were:
  - o Peri-operative data (Operating time, flap weight, clips, perforators, fluid)
  - o Inflammatory markers in drain fluid (day 0,1 and 2)
  - o Pain scores (0 to 10) and morphine use (mg)
  - o Mobility (number of steps)
  - o Abdominal wound assessment (AIRE score)
  - o Total abdominal drain fluid output (mL)
  - o Complications (flap problems, haematoma, seroma, abdominal wound healing problems)

Objectives

- Recruit a minimum of 106 breast reconstruction patients onto the trial
- Randomise the patients to either have the abdominal flap raise done with the conventional diathermy or PEAK PlasmaBlade™.
- Blinded collection of primary and secondary outcome values to allow objective comparison between the two groups through statistical analysis.
- Uni- and multivariable regression analysis to identify predictors and possible confounders for drain requirement, seroma presence and complications.

CHAPTER 2: MATERIAL AND METHODS

2.1 Study design

This clinical study was designed and conducted as a double blinded randomised controlled trial, as for comparison of two different operating machines in a group of patients this will result in the highest level of evidence, while excluding common causes of bias. Both patients and me, the research fellow were blinded to which machine was used in theatre. The surgeons were not blinded, but not involved in collection of any data. The blinding was broken after the last patient had completed her follow-up. Patients were informed via a letter about the type of operating machine (conventional diathermy or PEAK PlasmaBlade™) that was used for their abdominal flap harvest. The study was conducted between November 2016 and May 2018 in a single centre, St. Andrew's Centre for Plastic Surgery and Burns in Broomfield Hospital, in Chelmsford United Kingdom. The DIEP and MS-TRAM breast reconstruction patient population was selected for this trial because of the high number of cases performed on a yearly basis in the unit. Secondly, this procedure creates a large wound surface and can therefore serve as a good model to compare the effects of two different operating machines. Due to the mentioned large number of abdominal based breast reconstructions, even a small reduction in hospital stay and/or complications could have a significant influence on costs and bed availability for the department, making this a valuable population to study. Patients of two different consultants in plastic surgery were included into the study, Mr Venkat Ramakrishnan (VR) and Mr Matthew Griffiths (MG).

No changes were made to the study protocol after trial commencement.

2.2 Patient recruitment

Patients scheduled for a unilateral DIEP breast reconstruction, meeting the in-/exclusion criteria (Table 2.1), were informed about the study by the normal care team during their first clinic appointment. If the patient agreed, the research fellow would give further details, answer any questions and supply the patient with the information leaflet. On the day before surgery

the patient would be approached again and if willing to participate in the trial an informed consent would be obtained.

To eliminate factors that could delay wound healing, patients that were active smokers, patients suffering from diabetes, patients suffering from ischaemic heart disease, immuno-suppressed patients and/ or patients using steroid medication were excluded. To reduce the risk of post-operative bleeding patients with clotting disorders were excluded from the study. Exclusion based on BMI, age, immune-suppression, active smoking or pregnancy was not required for this study. The most common reason patients could not be recruited onto the trial was the need for a bi-pedicled DIEP/MS-TRAM breast reconstruction.

Table 2. 1 In-/exclusion criteria

Inclusion Criteria	**Exclusion criteria**
Adult (18-80 years) able to consent	Children (<18yrs) Adults older than 80 years
Unilateral immediate or delayed DIEP/ MS-TRAM breast reconstruction	Bilateral or bi-pedicled DIEP/ MS-TRAM breast reconstructions
BMI >20	BMI < 20
	Diabetic
	Immuno-suppression
	Ischaemic heart disease
	Clotting disorders
	On steroid medication
	Pregnancy
	Active smoking

2.3 Randomisation

The Anglia Ruskin Clinical Trial Unit (ARCTU) at Anglia Ruskin University (ARU) organised access to the randomisation service of the Trans European Network for Clinical Trials Service (TENALEA). This is an internet-based randomisation system that can be accessed 24 hours a day. Enrolled patients underwent a 1:1 block randomisation. The system stores the pre-determined sequence of randomisation. After consent was obtained by the research fellow randomisation was carried out by the normal care team, either the day before or the morning of surgery. The patient was either allocated to the ‘Group A - diathermy’ or ‘Group B - PEAK

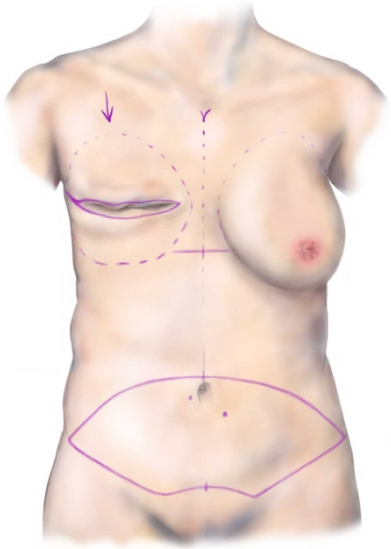
PlasmaBlade™. The results of the randomisation were sent via a confirmation email to senior author (MG) and his secretary and selected members of ARCTU. The research fellow, responsible for the post-operative data collection and the patients were blinded to the randomisation and surgical machine used. The blinding was broken after the last patient had completed the 6-week follow-up period.

2.4 Surgical procedure

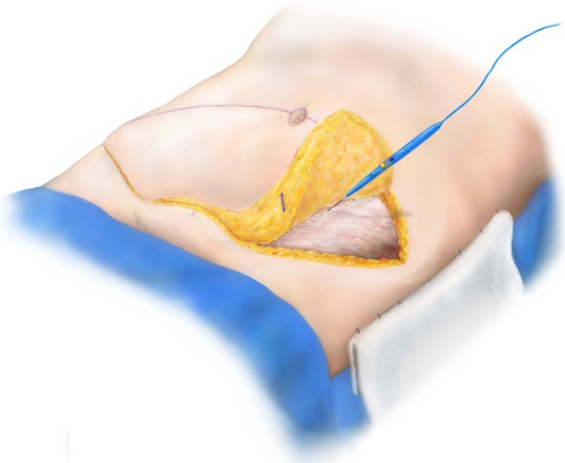
All patients underwent a standard DIEP or MS-TRAM breast reconstruction procedure (Figure 30). On induction, every patient received prophylactic intravenous antibiotics and 1 gram of tranexamic acid. A scalpel was used to make the skin incision to the depth of the dermis. The raising of the flap was subsequently done either using the PEAK Plasma Blade™ or conventional diathermy. The standardised maximum settings for the diathermy were cutting 40 Watt, coagulation 40 Watt and for the PEAK PlasmaBlade™ cutting 7 (35 Watt), coagulation 7 (35 Watt) (Appendix 1 – PEAK PlasmaBlade™ settings). If the bipolar was used for haemostasis it was not used above 15 Watt.

During the operation data recorded as part of the normal protocol were the flap raise time (min), number of clips used to seal off small blood vessels, the total weight of the flap, the number of blood vessels supplying the flap (perforators raised) and the amount of fluid given during the surgery (mL Hartmann's solution and/ or Volpex®). An Ultrapro mesh (Ethicon monocryl/proline composite) was placed underneath the abdominal fascia before it was closed with a 1 Stratafix™ suture. Before the abdominal closure two 15 French Blake drains were inserted and secured to the skin with a 2.0 Silk suture and connected to a low vacuum wound drainage system (85 kPa/neg 100mmHg). For the closure of the deep abdominal layer/ Scarpa's fascia 2.0 Vicryl® was used and for skin closure a subcutaneous 3.0 Stratafix™. The abdominal scar was sealed with Prineo™ tape and Dermabond® and finally covered with blue gauze and an abdominal binder (9-inch, Marena).

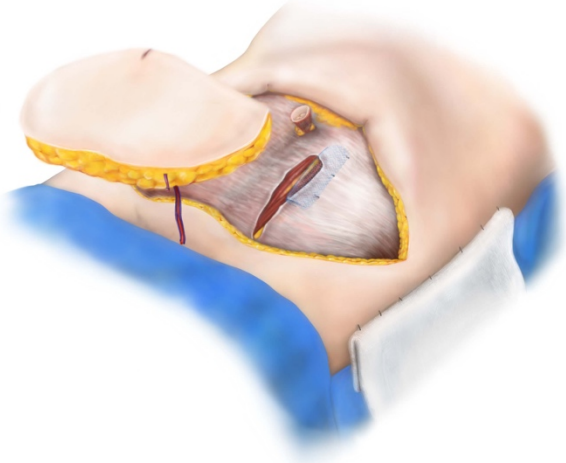
Figure 31 Steps of a delayed free autologous deep inferior epigastric perforator breast reconstruction flap.



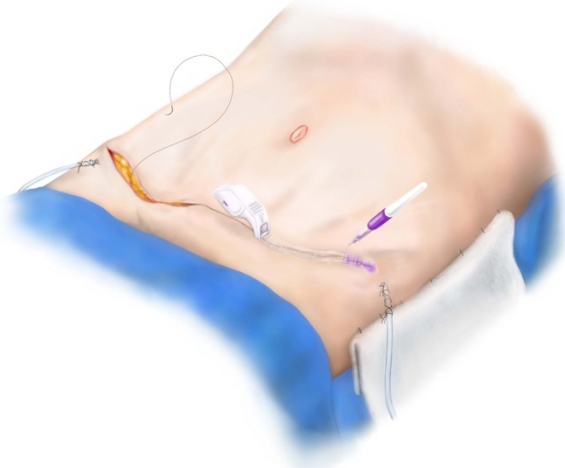
a. Pre-operative markings for a delayed right sided DIEP breast reconstruction flap



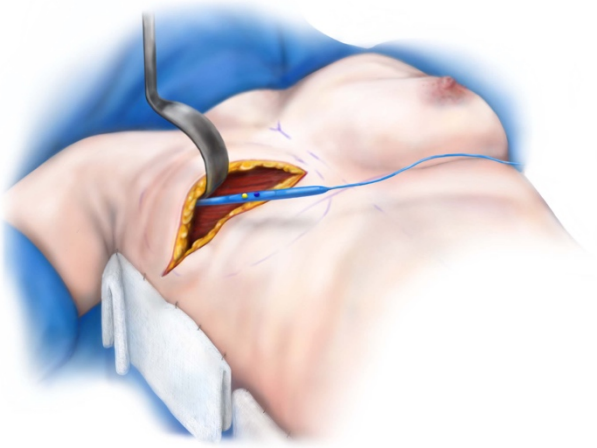
b. Raise of DIEP flap, containing skin and fat off the abdominal wall using electrosurgery



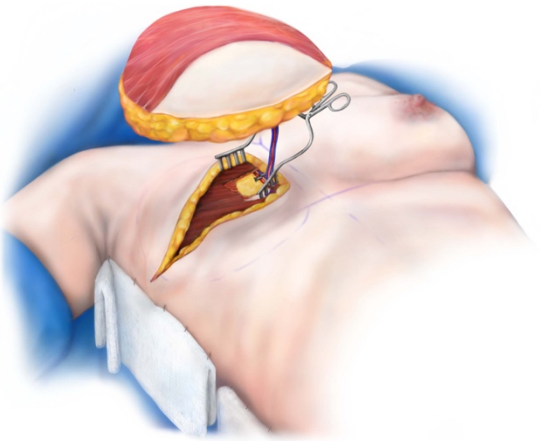
c. Raised DIEP flap with attached vessels, which was dissected out from between the rectus abdominis muscle. The fascial defect will be closed with a mesh and sutures

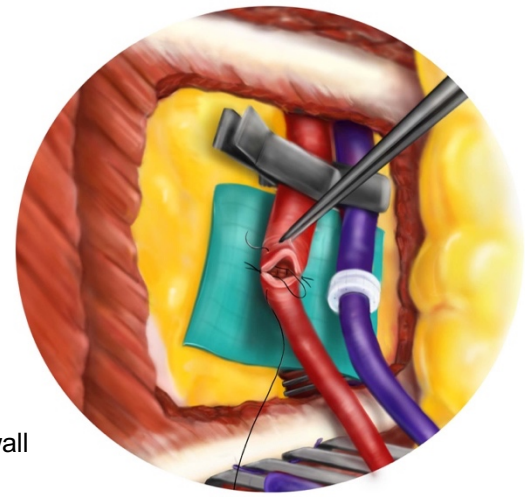


d. Closure of the abdominal donor site with dissolvable sutures and skin glue after insertion of two abdominal drains

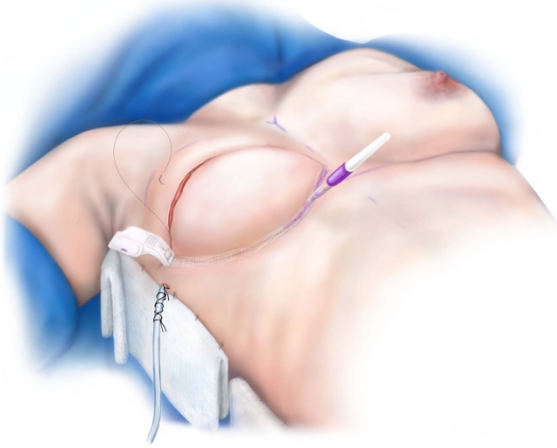


e. Creation of the chest wall skin pocket for the DIEP flap

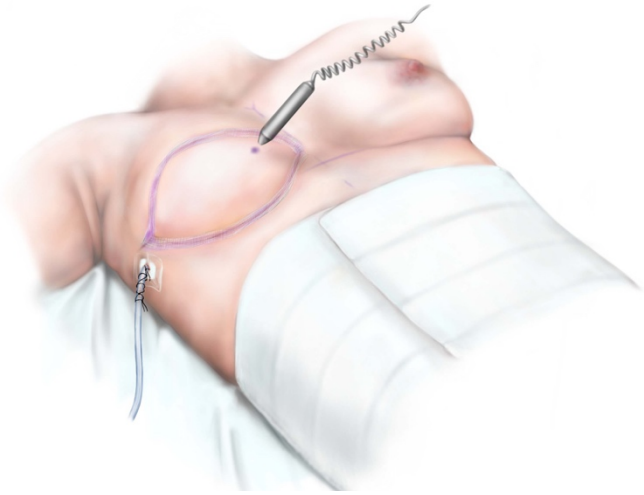




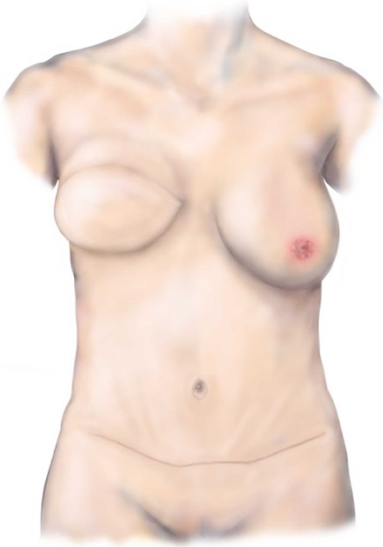
f. Microsurgical connecting of flap vessels to chest wall vessels



g. Insertion of flap into the skin pocket and closure with sutures and skin glue



h. Post-operatively an abdominal binder is applied. The flow in the anastomosed blood vessels can be checked with a handheld Doppler



i. Result after a delayed right sided DIEP breast reconstruction

Drawings by Miss Julia Ruston

2.5 Post-operative DIEP/ MS-TRAM protocol

Post-operative patients were monitored in a high dependency unit (HDU) setting. Depending on clinical circumstances, each patient would follow the same standard departmental free flap protocol (Table 2.2).

Table 2. 2 DIEP/ MS-TRAM protocol

Day -1 (Pre-operative)	• Pre-operative bloods and group and save • Clerking • Drug chart • Clexane 40 mg subcutaneous (sc) into inner thigh and thromboembolism-deterrent (TED) stockings for deep venous thrombosis (DVT) prevention
Day 0	• First 4 hours 30 minutes flap observations, after that 1 hourly • Cardiovascular observations 1 hourly • Sips of water, oxygen via nasal spec's, Bair Hugger (warmer), urine catheter • Monitor urine and drain output • Clexane 40 mg sc, TED stockings and flowtrons for DVT prevention
Day 1	• One hourly flap and cardiovascular observations • Review by team in the morning, if all well can eat and drink • Sit out in the chair with bra on • Haemoglobin level check • Physiotherapist input: encouraging deep breathing exercises and leg movement • Clexane 40mg sc, TED stockings and flowtrons for DVT prevention
Day 2	• Two hourly flap and cardiovascular observations • Start mobilising, if able to walk to toilet removal of urine catheter • Clexane 40mg sc and TED stockings for DVT prevention
Day 3	• Three hourly flap and cardiovascular observations • Assisted shower • Start removal of drains if 30mL or less in 24 hours and mobilising • Mobilisation • Clexane 40mg sc and TED stockings for DVT prevention
Day 4 till discharge	• Four hourly flap and cardiovascular observations • Independent shower • Removal of drains if 30 mL or less in 24 hours • Mobilisation • Clexane 40 mg sc and TED stockings for DVT prevention
Discharge with drain	• In case a patient was discharged with a drain they would call the ward every morning informing us about the drain out-put (ml/24h). Drains were removed in the hospital if draining 30 mL or less over 24 hours.

2.6 In-patient follow-up

During the post-operative inpatient period, the research fellow would see the patients every day, twice a day to collect the data (Figure 32).

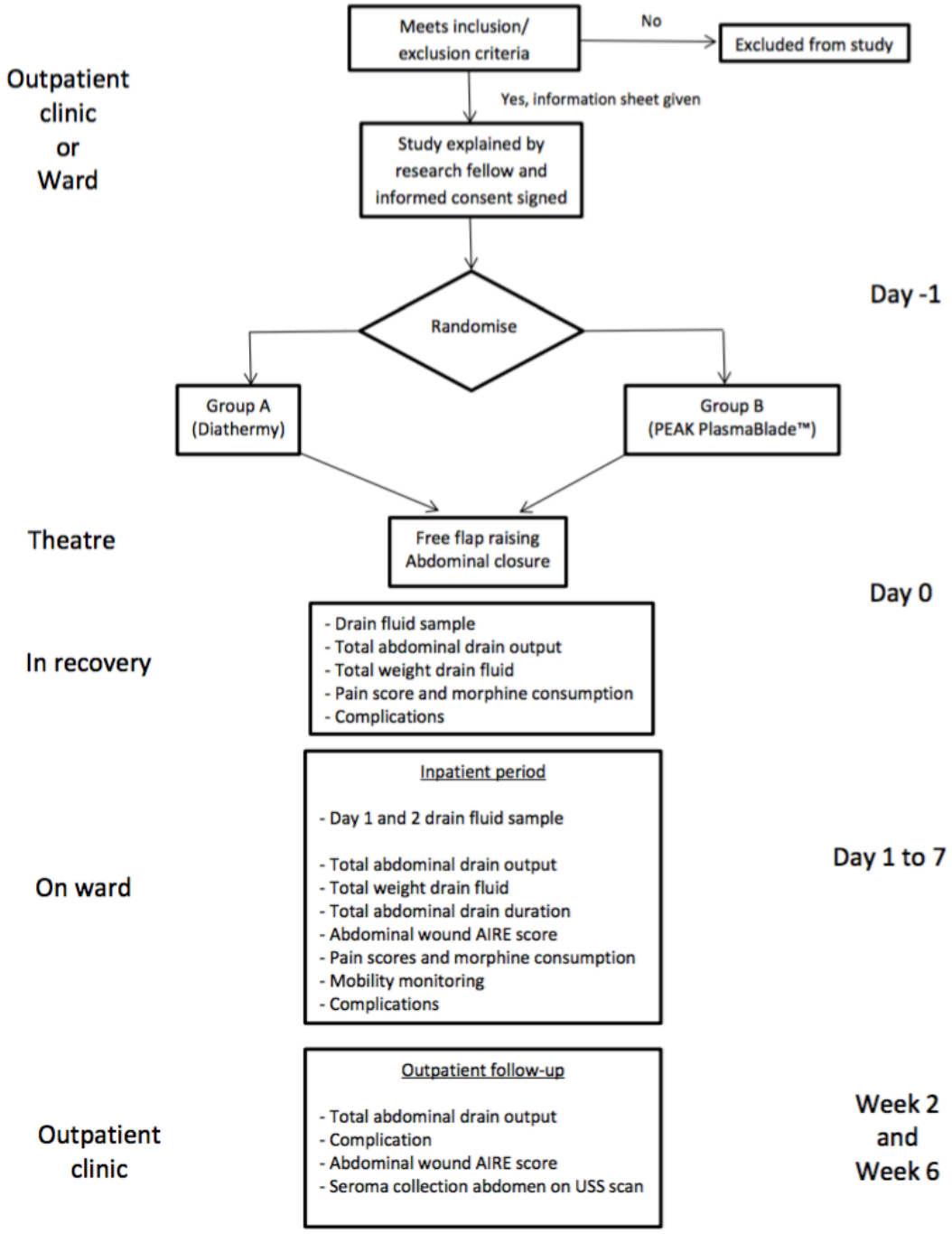


Figure 32: Flow-chart patient follow-up

2.6.1 Drain fluid samples

On the day of surgery and on post-operative days one and two, 3 mLs of drain fluid was obtained from one of the abdominal drain tubes using a three-way tap and a 10 to 100 mL syringe. Only 125 µL of drain fluid was required for the analysis, but because such small amounts are difficult to measure it was decided to use 1.5 mL Eppendorf tubes which were available from Broomfield hospital laboratory. The sample was transferred into two 1.5 mL Eppendorf tubes, one being the back-up sample. All tubes were stored in a -80°C freezer in the laboratory of Broomfield hospital. The samples were sent to Myriad RBM, Inc. a clinical laboratory improvement amendments (CLIA) certified biomarker testing laboratory located in Austin, Texas (United States). CytokineMAP A analysis (appendix 2 – M&M of analysis) was performed on the samples providing a quantitative measurement of key cytokines (Table 2.3) involved in inflammation, immune response and wound healing. The Cytokine MAP-A was deemed the most suitable of the offered packages as it includes most important inflammatory markers. Individual testing of a select number would have resulted in higher costs. After analysis only the cytokines bold in Table 2.3 were of measurable height and therefore included in the statistical analysis.

Table 2. 3 CytokineMAP A inflammatory cytokines.

Granulocyte-Macrophage Colony-Stimulating Factor	**Interleukin-8**
Interferon gamma	**Interleukin-10**
Interleukin-2	**Interleukin-18**
Interleukin-3	**Macrophage Inflammatory Protein-1 alpha**
Interleukin-4	**Macrophage Inflammatory Protein-1 beta**
Interleukin-5	**Monocyte Chemotactic Protein 1**
Interleukin-6	**Tumour Necrosis Factor alpha**
Interleukin-7	Tumour Necrosis Factor beta
*Cytokines in bold were included in the statistical analysis for this study	

After half of all the samples were collected in November 2017, the first batch was transported by World Courier on dry ice (-80°C) to Myriad RBM, Inc. in Austin, Texas. During the first analysis one of the samples was insufficient. We were able to send the back-up sample with the second batch in April 2018, resulting in the analysis of all 324 drain samples. The Myriad clinical laboratory guarantees highly reproducible results by the use of automated systems and processes in a tightly controlled environment. The cytokine analysis results were emailed in an excel file. For each cytokine, the least detectable dose (LDD) was given, this value was determined as the mean +3 standard deviation of 20 blank readings. Results below the LDD are expected to be more variable compared to results above. The lower limit of quantitation (LLOQ) represents the lowest concentration of cytokine that can be reliable detected (meeting the laboratory's requirements for accuracy). When reviewing Table 2.4 there is a clear difference between the LDD and LLOQ between the 2017 and 2018 measurements for most cytokines. The laboratory has confirmed these differences are not caused by the calibration of the machines used for the analysis.

Table 2. 4 Cytokine Least Detectable Dose (LDD) and Lower Limit of Qualification (LLOQ) levels in 2017 and 2018 analysis

Cytokine	LDD_{2017}	$LLOQ_{2017}$	LDD_{2018}	$LLOQ_{2018}$
Interleukin-4 (pg/mL)	50	26	36	45
Interleukin-6 (pg/mL)	3.4	2.9	2.3	4.1
Interleukin-7 (pg/mL)	25	30	41	28
Interleukin -8 (pg/mL)	8.2	7.9	3.8	3.2
Interleukin-10 (pg/mL)	3.2	7.1	2.9	5.5
Interleukin-18 (pg/mL)	48	56	37	30
Macrophage Inflammatory Protein-1 alpha (pg/mL)	50	37	48	34
Macrophage inflammatory Prottein-1 beta (pg/mL)	62	44	34	41
Monocyte Chemotactic Protein 1 (pg/mL)	134	112	138	135
Tumour Necrosis Factor alpha (pg/mL)	16	20	27	62

LDD: Least Detectable Dose; LLOQ: Lower Limit of Qualification
pg/mL = pictogram/ millilitre; ng/mL = nanogram/millilitre

2.6.2 Abdominal drain output

While the patients were admitted to the hospital the abdominal drain output was measured twice a day, morning and evening. The total amount of fluid (mL) in the bottle was noted down, also the weight of the drain bottles was measured and subtracted from the weight of the empty bottle. Drains were removed when draining 30 mL or less in 24 hours. In some cases, drains fell out accidentally or were removed earlier for clinical reasons. In case of prolonged high drain output, patients were occasionally discharged home with one abdominal drain. If this was the case patients were asked to call into the hospital every morning after reviewing the total amount of drain fluid in the bottle. If the drain fluid production had reached 30 mL or less in 24 hours the patient would return to the hospital where the drain was removed.

2.6.3 Pain and morphine consumption

Twice a day, patients were asked to score their pain or discomfort using the numerical rating scale (NRS) with 0 being no pain at all and 10 the worse pain imaginable. Every patient was given daily paracetamol and ibuprofen for pain control. For breakthrough pain patients could request 5 to 10 mg of liquid morphine (Oramorph). Its use was discouraged as it often causes sickness, drowsiness and constipation. Daily total morphine (Oramorph in mg) consumption was extracted from the drug chart.

2.6.4 Abdominal wound assessment

Once daily the abdominal wound was assessed using the Acute Inflammatory Response Evaluation (AIRE) score (Richter et al., 2012). This evaluates the wound on the following aspects: erythema (redness), oedema (swelling), pain and local temperature. Scoring them 0 to 3 (Table 2.5) resulting in a total score between 0 to 12.

Table 2. 5 Acute inflammatory response evaluation (AIRE) (Richter et al., 2012)				
Score	Erythema	Oedema	Pain	Local temperature
0	Non-observed	Non-observed	None	No change
1	Slight blanching or redness along incision closure line	Slight increase in tissue firmness along the wound closure line	Pain along the wound closure line with pressure	Slightly warmer compared to adjacent skin
2	Moderate redness extending <2mm on either side of wound	Pitting of the skin around the incision with mild pressure	Pain at the site with touch	Definitely warmer compared to adjacent skin
3	Intense redness extending >2mm	Tense firmness around the wound	Continuous pain	Radiating heat around wound site

2.6.5 Mobility

Patients started mobilising from the second post-operative day, to reduce their risk of developing a deep venous thrombosis (DVT) or pulmonary embolism (PE). They were provided with a pedometer (Willful Fitness Activity Tracker Watch) to give an estimation of daily mobility (number of steps).

2.6.6 Complications

Any complications during the inpatient period such as bleeding, infection, flap problems and problems in abdominal wound healing were registered.

2.7 Out-patient follow-up

Following their discharge patients were seen in our outpatient department after two and six weeks. The timing of these appointments was chosen to be in concordance with the regular follow-up appointments, avoiding extra appointments for the study participants. The week two was a nurse led clinic appointment and week six was a consultant led clinic appointment. At both follow-up appointments, data on complications and abdominal AIRE scores were recorded. An abdominal ultrasound was performed by the research fellow using the V-Universal™ Stand portable ultrasound machine produced by SonoSite, Inc.

With the patient flat on an examination table with the head slightly raised the nine regions of the abdomen (Figure 33) were systematically examined for fluid collections (seromas).

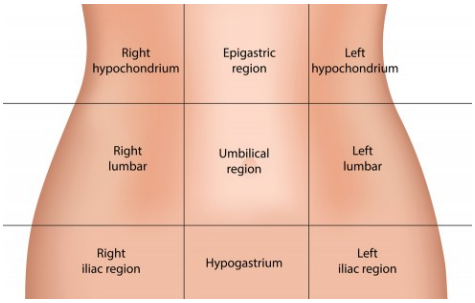


Figure 33 Nine regions of abdomen

If a seroma was identified the dimensions were measured (length, width and maximum height in cm) and recorded. To estimate the volume of the identified fluid collections half of the volume of an ellipsoid was used (Figure 34).

$$\frac{4}{3}\pi\ abc$$

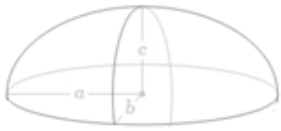


Figure 34 Formula to calculate the volume of an ellipsoid

Almost all seromas were treated conservatively and only drained (Figure 35) if they were causing discomfort for the patient.

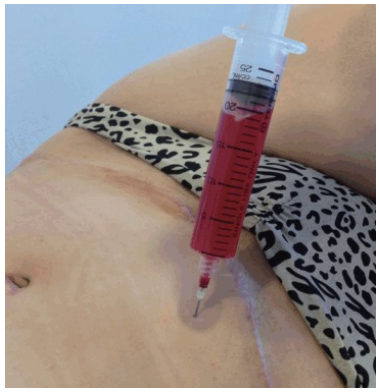


Figure 35 Drainage of abdominal seroma collection through needle aspiration (Vidal, Berner, & Will, 2017)

After completion of the 6-week follow-up period patients were discharged from the study. No changes to trial outcomes were made after trial commencement.

2.8 Statistics and analysis

Using data from the in our unit conducted pilot study comparing the PEAK PlasmaBlade™ to conventional diathermy in 40 DIEP patients (Chow, Oni, Ramakrishnan, & Griffiths, 2019), looking at total drain output (mL) and amount of days drains were required a power calculation was performed.

For the pilot study using the independent sample t-test, the mean number of days the drain was required in the diathermy group was 5.55 days with a standard deviation of 1.00 and 6.70 days with a standard deviation of 2.36 in the PEAK PlasmaBlade™ group.

In order to detect a significant difference in abdominal drainage duration based on a 5% significance level to give a power of 80% using Lehr's formula[2]:

$$\frac{16}{(Standardized\ difference)^2} = \frac{16}{0.30}$$

The standard difference was calculated by $\frac{\delta}{\sigma}$ with δ being the smallest difference in mean which is clinically important and σ the assumed equal standard deviation of the observations in each of the two groups. The smallest difference in mean to be clinically important was set on 1 day, as a 1-day reduction in drain requirement would lead to earlier discharge, reducing costs on hospital stay. This would also increase turn-over resulting in the ability to treat more patients.

The pooled standard deviation was used for the σ, using the formula:

$$\sigma = SD_{pooled} = \sqrt{\frac{(SD_1^2 + SD_2^2}{2}} = \sqrt{\frac{1^2 + 2.36^2}{2}} = 1.81$$

This results in a minimal sample size of 53 patients for each group (106 overall).

To determine if collected continuous data was normally distributed the Shapiro-Wilk test was performed. If normally distributed the independent samples t-test was used to establish if there was a statistically significant difference between the two groups. If the data was not normally distributed the Mann-Whitney U Test was used.

To calculate statistical significance for categorical data the Pearson Chi-Square Test for numbers over 5 was used. If the count was equal to or less than 5 the Fisher's Exact Test was used. Categorical data were: consultant (VR/MG), procedure (DIEP/MS-TRAM), adjuvant therapy (radiotherapy/ neo-adjuvant chemotherapy/ hormone therapy) and complications.

For the primary outcome value three analysis were conducted because drains were incorrectly removed in 19 occasions (accidental or due to clinical reasons). First the incorrectly removed day of drain removal was kept into the analysis, secondly the patients with an incorrect drain removal were excluded from the analysis and thirdly multiple imputation was applied where incorrect drain removal days were replaced.

Linear regression (Cox proportional hazard model) was used to identify significant determinants for the time to drain removal. Variables that had a significant p-value in the univariate analysis were included in a multivariable analysis. Significant determinants could indicate confounding factors for which would be corrected.

Logistic regression was used to identify determinants for complications and the presence of seroma at the 2- and 6-week abdominal ultrasound scan. Variables that had a significant p-value in the univariate analysis were included in multivariable analysis, if none of the determinates were significant p values <0.10 were included in the multivariable analysis. Significant determinants could indicate confounding factors for which would be corrected.

A value below or equal to 0.05 (2-tailed) was considered to be statistically significant.

Blinding made it impossible to perform an interim analysis.

2.9 Ethics

Patients were given the option to participate in this study, it was emphasised participation was voluntary, and refusal would not affect their care in any way. Patients participating in this

randomised controlled trial were given the regular post-operative care, only the harvest of the abdominal free flap was either done with conventional diathermy or the PEAK PlasmaBlade™. No extra invasive tests were required. The drain fluid was collected from the abdominal drain tube and non-invasive ultrasound was used to detect any abdominal seroma formation. Patients could choose to leave the study at any time without a required reason, which was not experienced.

Before commencing the study, the research fellow and both Plastic surgeons Mr Griffiths and Mr Ramakrishnan completed the "Good Clinical Practice (GCP)": eLearning module, which gives a practical guide to ethical and scientific quality standards in clinical research.

Organisation that evaluated the study protocol and rewarded ethical approval:

- The East of England - Cambridge Central Research Ethics Committee (REC reference: 16/EE/0005, Protocol number: 137680 and IRAS project ID: 192471). Approval was acquired on the 11th February 2016.
- The Research and Development (R&D) department of Mid Essex Hospital Services NHS Trust (MEHT). Approval was acquired on the 19th August 2016.
- The Faculty of Medical Science Research Ethics Panel (FREP) of the Anglia Ruskin University (ARU) ethical application (FREP number: 16/17 086). Approval was acquired on the 24th February 2017.

During the study course the Cambridge Ethics Committee which is part of the Health Research Authority, was contacted in February 2017 to inform if it would be allowed to collect data for the study if there were additional hospital visits by patients for clinical reasons. This amendment was deemed non-substantial and it was therefore not necessary to make formal adjustments to the protocol.

2.10 Financing

The study received monetary support from Medtronic. The first part (£56,652) was given at the start of the study and the second part (£37,229) after delivery of the final study results. The PEAK Plasma generator and blades were provided free of charge by Medtronic. The funder was not involved in the study design, in the collection, analysis and interpretation of data, in writing of the manuscript; or in the decision to submit the manuscript for publication.

CHAPTER 3: RESULTS

3.1 Baseline characteristics of the study population

During the 19-month recruitment period (between November 2016 and May 2018), 119 patients were recruited. Two patients were accidentally randomised twice because of a glitch in the computer system, resulting in a total number of 121 randomisations. For these two patients the result of the first randomisation was used and the second one deleted by the operator. Eleven patients were excluded from the study following clinically necessary pre- or peri-operative diversion from the protocol not caused by the surgical instrument used (Table 3.1). Resulting in a final study population of 108 patients.

Table 3. 1 Reasons for exclusion from study

Study number	Group	Day of exclusion	Reason for exclusion
1010030	CD	0	Repair of abdominal hernia with mesh
1010057	CD	0	Bi-pedicled DIEP
1010080	CD	0	Bi-pedicled DIEP
1010081	CD	0	Different operating consultant
1010083	PPB	0	Bi-pedicled DIEP
1010104	CD	0	Bi-pedicled DIEP
1010105	CD	0	Different operating consultant
1010106	PPB	0	Operation cancelled
1010107	PPB	0	Bi-pedicled DIEP
1010117	CD	0	Bi-pedicled DIEP
1010119	PPB	0	SIEA flap performed

PPB = PEAK PlasmaBlade™; CD= Conventional diathermy

Fifty-two patients were randomised to the conventional diathermy and 56 to the PEAK PlasmaBlade™ group. The baseline characteristics of the two groups are shown in table 3.2. Age, height, weight and BMI were comparable between the two different groups. The patients were evenly distributed between the two operating consultants and two procedures (DIEP and MS-TRAM), axillary sampling or clearance and procedures on the ipsilateral side. The requirement for (neo-) adjuvant cancer treatment (radiotherapy, neo-adjuvant chemotherapy and/ or hormone therapy) were equal between the two groups.

Table 3. 2 Patient baseline characteristics for the two study groups

Characteristic	Conventional diathermy (n=52)	PEAK PlasmaBlade™ (n=56)	p-value
Age (yr.) †	52.5 (45.0 – 62.8)	52 (44.0 – 60.0)	0.44
Height (cm) †	161 (154.3 – 168.6)	163 (158.0 – 169.0)	0.32
Weight (kg) *	76.8 ± 12.1	75.0 ± 13.5	0.44
Body mass index†	28.6 (26.0 – 32.6)	27.7 (24.7 – 31.38)	0.14
Consultant (MG/VR)	17/35	16/40	0.68∂
Procedure (DIEP/MS-TRAM)	50/2	52/4	0.68Δ
Timing (immediate/delayed)	39/13	43/13	0.83∂
Axillary clearance	21.2%	32.1%	0.20∂
SLNB	11.5%	10.7%	0.90∂
Procedure ipsilateral breast	34.6%	28.6%	0.50∂
Pre-op radiotherapy	28.8%	28.6%	1.00∂
Neo-adjuvant chemotherapy	21.2%	25%	0.66∂
Hormone Therapy	28.8%	26.8%	0.83∂

* Mean ± SD; Independent samples t-test
† Median (IQR); Mann-Whitney U test
∂ Pearson Chi-Square test
Δ Fisher's Exact test
SLNB = sentinel lymph node biopsy
SD = Standard Deviation; IQR = Interquartile Range

3.2 Peri-operative data

Table 3.3 shows the data collected during the operation with either of the two different operating machines.

Table 3. 3 Peri-operative data

Characteristic	Conventional diathermy (n=52)	PEAK PlasmaBlade™ (n=56)	p-value
Time flap raise (min) †	129.0 (90.0 – 159.3)	120.0 (93.5- 154.5)	0.80
Number of perforators†	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.47
Number of vessel clip packs†	12.0 (9.0 – 25.0)	12.0 (9.0 – 14.0)	0.63
Flap weight (g) †	958.5 (759.0 – 1239.0)	833.0 (575.0 – 1031.0)	0.03
Amount of IV fluid given (L) †	2.0 (1.8 – 2.5)	2.0 (2.0 – 2.5)	0.41

†Median (IQR); Mann-Whitney U test
IV = Intravenous; min = minutes; mg = milligram; L = litre

There was no statistically significant difference in time (min) to raise the abdominal flap (p=0.80) using either of the two different machines. The number of perforators taken to supplying the abdominal flap did not statistically significantly differ (p=0.47) between the two groups. The number of vessel clips used during the procedure to clamp arteries and veins did not differ significantly (p=0.63). The flap weight (gram) of the removed abdominal flap did significantly differ (p=0.03) between the two groups, being higher in the conventional diathermy group. The amount of intravenous fluid (L) given during the operation (Hartmann's solution and Volpex®) did not show a statistically significant difference (p=0.41).

3.3 Inflammatory cytokines

Drain fluid samples collected on day 0,1 and 2 were analysed to determine if there were significant differences between levels of inflammatory cytokines produced after operating with either of the two operating machines. Levels of the inflammatory cytokines' TNF-alpha, IL-4, IL-6, IL-8, IL-10, IL-18, MIP-1 alpha, MIP-1 beta and MCP-1 at the three different days can be found in table 3.4.

Table 3. 4 Inflammatory Cytokines in drain fluid on day 0,1 and 2

	Cytokine	Conventional diathermy (n=52)	PEAK PlasmaBlade™ (n=56)	p-value
Day 0	**TNF-alpha†**	62.0 (20.0 – 62.0)	62.0 (20.0 – 62.0)	0.41
	IL-4†	45.0 (26.0 – 45.0)	45.0 (26.0 – 45.0)	0.85
	IL-6†	28150.0 (8777.5 – 55875.0)	26600.0 (7552.5 – 46200.0)	0.40
	IL-8†	8450.0 (23253.0)	9695.0 (19828.0)	0.90
	IL-10†	56.5 (36.5 – 93.0)	49.5 (35.3 – 67.5)	0.29
	IL-18†	444.5 (353.8 – 630.8)	447.0 (325.5 – 610.0)	0.81
	MIP-1 alpha†	83.5 (57.3 – 139.5)	77.5 (55.8 – 125.8)	0.50

	Cytokine	Conventional diathermy (n=52)	PEAK PlasmaBlade™ (n=56)	p-value
Day 0	**MIP-1 beta†**	1500.0 (961.5 – 2200.0)	1215.0 (706.0 – 1705.0)	0.07
	MCP-1†	20550.0 (9952.5 – 48175.0)	23050.0 (8447.5 – 42400.0)	0.70
Day 1	**TNF-alpha†**	62.0 (22.0 – 62.0)	62.0 (22.0 – 62.0)	0.91
	IL-4†	43.5 (26.0 -45.0)	45.0 (26.0 – 45.0)	0.69
	IL-6†	36150.0 (23175.0 – 47325.0)	38650.0 (21450.0 – 48025.0)	0.90
	IL-8†	20600.0 (9795.0 – 52175.0)	18900.0 (9012.5 – 31075.0)	0.53
	IL-10†	127.0 (86.8 – 170.3)	119.0 (88.5 – 144.5)	0.51
	IL-18†	443.5 (290.5 – 577.8)	362.0 (258.0 – 523.5)	0.18
	MIP-1 alpha†	84.0 (58.0 – 151.5)	68.5 (50.0 – 103.3)	0.054
	MIP-1 beta†	2210.0 (1197.5 – 3222.5)	1540.0 (895.0 – 2665.0)	0.20
	MCP-1†	33850.0 (21200.0 – 53375.0)	31100.0 (20525.0 – 53850.0)	0.86
Day 2	**TNF-alpha†**	62.0 (29.0 – 62.0)	62.0 (25.3 – 62.0)	0.48
	IL-4†	45.0 (19.0)	45.0 (19.0)	0.70
	IL-6†	19000.0 (9895.0 – 26850.0)	13650.0 (10067.5 – 18700.0)	0.10
	IL-8†	22950.0 (10425.0 – 50725.0)	17350.0 (10200.0 – 30075.0)	0.14
	IL-10†	115.5 (77.0 – 155.0)	104.5 (86.3 – 138.8)	0.78
	IL-18†	382.5 (243.0 – 517.3)	300.5 (222.8 - 431.5)	0.07
	MIP-1 alpha†	116.0 (80.0 – 181.8)	97.5 (79.0 – 155.0)	0.19
	MIP-1 beta†	2160.0 (1515.0 – 3487.5)	1920.0 (1390.0 – 3047.5)	0.31
	MCP-1†	35350.0 (22200.0 – 49250.0)	36500.0 (22700.0 – 55650.0)	0.96
† Median (IQR); Mann-Whitney U test				

None of the inflammatory cytokines differed significantly between the two groups on any of the three days. The levels of inflammatory cytokines MIP-1 beta on day 0 (p=0.07), MIP-1

alpha on day 1 (p=0.054) and IL-18 on day 2 (p=0.07) showed a tendancy towards lower levels in the PEAK PlasmaBlade™, almost reaching statistical significance.

3.4 Abdominal drains

Table 3.5 presents the median drain fluid volume (mL) and weight (mg) of the drain fluid for each group, the number of patients who went home with a drain and the primary outcome "number of days drains were required".

Table 3. 5 Abdominal drains	**Conventional diathermy (n=52)**	**PEAK PlasmaBlade™ (n=56)**	**p-value**
Volume drain fluid (mL) †	342.5 (233.8 – 618.8)	355.0 (228.8 – 532.5)	0.68
Weight drain fluid (mg) †	338.5 (219.3 – 596.5)	337.0 (221.8 – 531.5)	0.75
Discharge home with drain (%)	19%	29%	0.26∂
Number of days drains required all patients†	6.0 (5.0 – 8.8)	5.0 (5.0 – 8.5)	0.48
† Mann-Whitney U test; Median (IQR), ∂ Pearson Chi-Square test			

There was no statistically significant difference (p=0.68) between the total volume drained in the conventional diathermy group (342.5 mL) and the PEAK PlasmaBlade™ group (355.0 mL). Also, the weight of the drain fluid was equal between the two groups therefore not showing any statistically significant differences (p=0.75). Patients in both groups went home with the drain equally often, not reaching statistical significance (19.2% vs 28.6%, p=0.26). In the PEAK PlasmaBlade™ group the drains were required for 5 days compared to the 6 days in the conventional diathermy group, this did not reach statistical significance (p=0.48). In diagram 1.1 are two histograms showing the distribution of the amount of days the drains were required for the two different study groups.

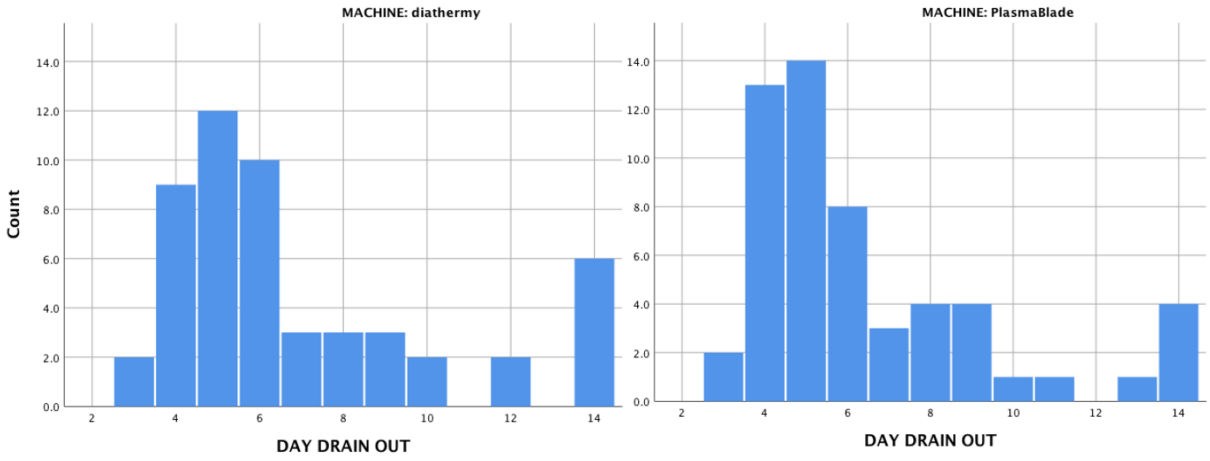


Diagram 1. 1 Histograms for the amount of days the drains were required. On the left for the diathermy (n=52) and on the right for the PEAK PlasmaBlade™ (n=56)

3.4.1 Exclusion of incorrectly removed drain values

In the normal diathermy group ten patient's drains accidentally came out or were removed for clinical reasons while draining over 30mL in 24 hours, in the PEAK PlasmaBlade™ group this was the case in nine patients. An analysis of the patient groups excluding these patients (drain removed draining >30 mL/ 24 hours) was performed. The results can be found in Table 3.6. Diagram 1.2 shows the adjusted histograms.

Table 3. 6 Patients with abdominal drains removed according to protocol (<30mL/24h)

	Conventional diathermy (n=42)	**PEAK PlasmaBlade™ (n=47)**	**p-value**
Cases excluded based on too early drain removal (>30 mL/ 24h)	10	9	
Number of days drains required†	6.0 (5.0 – 9.0)	5.0 (4.0 – 8.0)	0.17
† Mann-Whitney U test; Median (IQR)			

The median number of days the drains were required in both groups was the same as in the cohort of all patients.

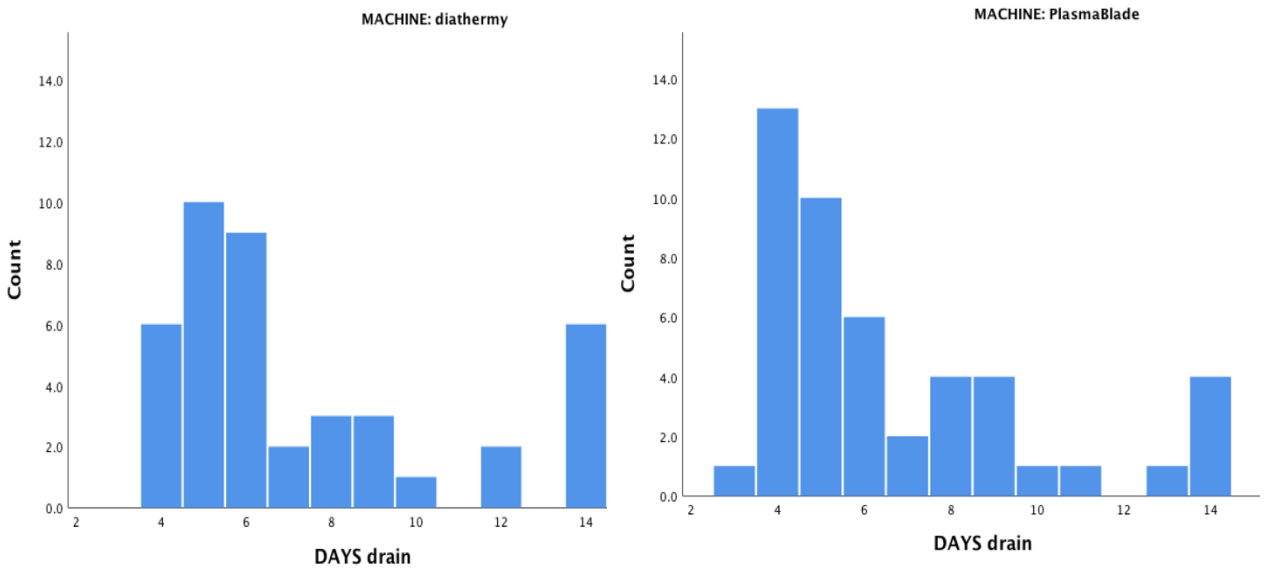


Diagram 1. 2 Histograms for the amount of days the drains were required after excluding too early drain removal (>30mL/24h). On the left for the diathermy (n=42) and on the right for the PEAK PlasmaBlade™ (n=47)

Table 3.7 shows the baseline characteristics for the cohort of 89 patients (after exclusion of patients that had their drain removed too early >30 mL/ 24 hours). Like in the total study population, the difference in flap weight (p=0.006) is the only significant variable.

Table 3. 7 Characteristics patients excluding drain removed >30mL/24h

Characteristic	Conventional diathermy (n=42)	PEAK PlasmaBlade™ (n=47)	p-value
Age (yr.) †	53.5 (44.8 – 63.0)	52.0 (44.0 – 62.0)	0.26
Height (cm) *	161.3 ± 8.1	162.7 ± 6.6	0.29
Weight (kg) *	76.3 ± 11.7	74.1 ± 13.1	0.41
Body mass index*	29.4 ± 4.3	27.9 ± 4.4	0.11
Consultant (MG/VR)	10/32	12/35	1.00∂
Procedure (DIEP/MS-TRAM)	40/2	43/4	0.68Δ
Timing (immediate/delayed)	34/8	37/10	1.00∂
Axillary clearance	21.4%	36.2%	0.16∂
SLNB	11.9%	10.6%	1.00Δ
Procedure ipsilateral breast	38.1%	29.8%	0.50∂
Pre-op radiotherapy	31.0%	23.4%	0.48∂
Neo-adjuvant chemotherapy	21.4%	25.5%	0.80∂
Hormone Therapy	31.0%	27.7%	0.82∂

	Conventional diathermy (n=42)	PEAK PlasmaBlade™ (n=47)	p-value
Time flap raise (min) †	122.0 (90.0 – 146.3)	120.0 (100.0- 154.0)	0.60
Number of perforators†	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.61
Number of vessel clip packs†	12.0 (9.0 – 14.3)	11.5 (10.0 – 15.0)	0.87
Flap weight (mg) *	979.1 ± 355.8	781.7 ± 305.7	0.006
Amount of IV fluid given (L) †	2.5 (2.0 – 2.5)	2.0 (2.0 – 2.5)	0.96

* Mean ± SD; Independent samples t-test
† Median (IQR); Mann-Whitney U test
∂ Pearson Chi-Square test
Δ Fisher's Exact test

3.4.2 Multiple imputation for missing data

Multiple imputation was performed for the incorrectly removed drains, considering them as missing data. Five imputations were performed. The independent samples t-test was used to identify a difference between the means of the pooled imputation drain data, which resulted in a non-significant p-value of 0.41, compared to the original data with missing values p=0.28. The Mann-Witney U test cannot be performed for the pooled data, but only for each separate imputation model resulting in p=0.53, p=0.17, p=0.32, p=0.12, p=0.21, compared to the original data with missing values p=0.17.

3.4.3 Kaplan-Meier curve

A Kaplan-Meier curve was created (Diagram 1.3). All patients were included, but the 19 patients who had their drains remove too early (draining more than 30 ml/ 24hours) were censored.

There was no statistically significant difference between the two groups using the Log Rank test, with a p-value of 0.42.

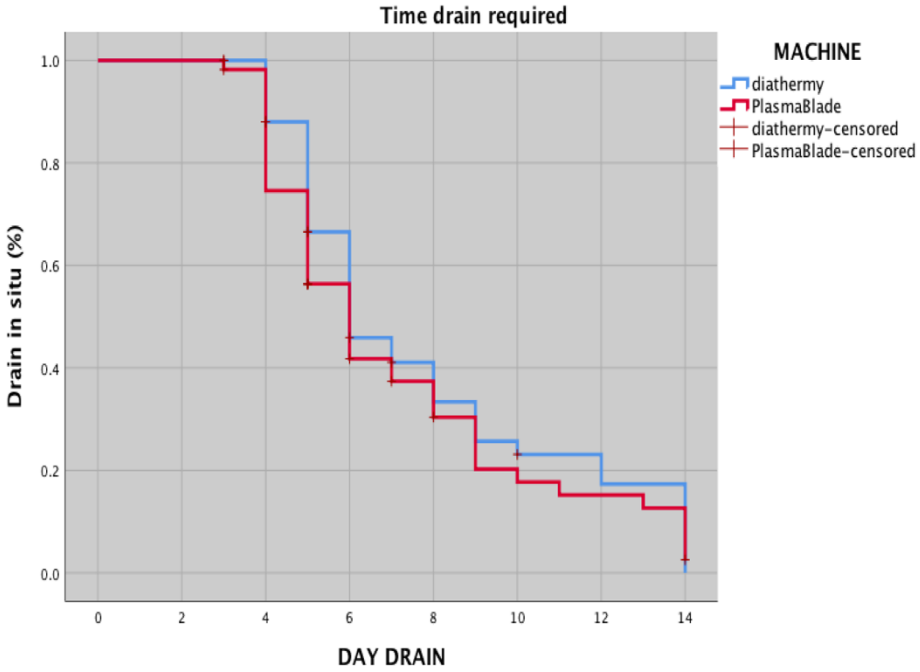


Diagram 1. 3 Kaplan-Meier curve for the amount of days the drains were required. Censored patients were shown with a cross.

3.5 Pain score and morphine use

Table 3.8 shows pain scores (0 – 10) and morphine (mg) use during the first seven days of admission. The number of patients decreases over the subsequent days due to discharge from the hospital.

Table 3. 8 Pain and Morphine use

		Conventional diathermy	PEAK PlasmaBlade™	p-value
Day 0	**Number of patients**	52	55	
	Pain†	2 (1.0 – 4.8)	4 (1.0 – 6.0)	0.02
	Morphine (mg) †	0 (0)	0 (0.0 – 5.0)	0.60
Day 1	**Number of patients**	50	56	
	Pain morning†	3.0 (2.0 – 4.8)	2.0 (1.0 – 5.0)	0.62
	Pain afternoon†	2.5 (1.0 – 4.3)	2.0 (1.0 – 5.0)	0.63
	Morphine (mg) †	5.0 (0 – 10)	0.0 (0 – 18.8)	0.77
Day 2	**Number of patients**	51	56	
	Pain morning†	2.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)	0.52
	Pain afternoon†	1.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)	0.77
	Morphine (mg) †	0 (0 – 10.0)	0 (0 – 5.0)	0.19

		Conventional diathermy	PEAK PlasmaBlade™	p-value
Day 3	**Number of patients**	50	54	
	Pain morning†	1.0 (1.0 – 3.0)	2.0 (1.0 – 4.0)	0.31
	Pain afternoon†	1.0 (1.0 – 3.0)	1.0 (0 – 2.0)	0.11
	Morphine (mg) †	0 (0)	0 (0)	0.78
Day 4	**Number of patients**	50	54	
	Pain morning†	1.0 (1.0 – 3.0)	1.0 (0 – 2.0)	0.16
	Pain afternoon†	1.0 (1.0 – 2.3)	1.0 (0 – 2.0)	0.77
	Morphine (mg) †	0 (0)	0 (0)	0.14
Day 5	**Number of patients**	44	43	
	Pain morning†	1.0 (1.0 – 2.0)	1.0 (0 – 2.5)	0.58
	Pain afternoon†	1.0 (1.0 – 1.0)	1.0 (0 – 2.0)	0.88
	Morphine (mg) †	0 (0 – 10.0)	0 (0)	0.16
Day 6	**Number of patients**	30	30	
	Pain morning†	1.0 (0.3 – 1.8)	1.0 (0.8 – 2.3)	0.68
	Pain afternoon†	1.0 (0 – 2.0)	1.0 (0 – 2.0)	0.63
	Morphine (mg) †	0 (0)	0 (0)	0.42
Day 7	**Number of patients**	12	14	
	Pain morning†	1.0 (0 – 2.0)	1.0 (0 – 2.0)	0.80
	Pain afternoon†	1.0 (0 – 1.3)	1.0 (0 – 3.5)	0.82
	Morphine (mg) †	0 (0)	0 (0)	0.72
†Median (IQR); Mann-Whitney U test				

The only statistically significant result was the median pain score post-operatively, in recovery (day 0). The PEAK PlasmaBlade™ group had a statistically significant (p=0.02) higher median pain score of 4 (IQR 1.0 – 6.0), compared to the normal diathermy group with a pain score of 2 (IQR 1.0 – 5.0).

3.6 Abdominal wound assessment (AIRE score)

From day 1 the abdominal wound was inspected and scored on a daily basis using the Acute Inflammatory Response Evaluation (AIRE) score, scoring between 0 and 12. As the AIRE scores were very low throughout the study population Table 3.9 shows the percentage of patients having an AIRE score ≥ 1 for day 1 till day 7.

Table 3. 9 Daily admission abdominal wound assessment (AIRE score)				
		Conventional Diathermy	**PEAK PlasmaBlade™**	**p-value**
Day 1	**Total number of patients**	52	56	
	Patients with AIRE score ≥1	1.9%	5.4%	0.62†
Day 2	**Total number of patients**	52	56	
	Patients with AIRE score ≥1	7.7%	8.9%	0.88†
Day 3	**Total number of patients**	52	56	
	Patients with AIRE score ≥1	9.6%	3.6%	0.22†
Day 4	**Total number of patients**	51	54	
	Patients with AIRE score ≥1	11.8%	3.7%	0.09†
Day 5	**Total number of patients**	45	43	
	Patients with AIRE score ≥1	15.6%	4.7%	0.13†
Day 6	**Total number of patients**	31	30	
	Patients with AIRE score ≥1	19.4%	6.7%	0.20†
Day 7	**Total number of patients**	13	14	
	Patients with AIRE score ≥1	38.5%	14.3%	0.33†
†Mann-Whitney U test; AIRE: Acute Inflammatory Response Evaluation				

There were no statistically significant differences between the low total AIRE scores throughout the admission comparing the two different groups, neither was there a difference between the individual aspects of the score (erythema, oedema, pain, temperature).

Table 3.10 shows the percentage of patients with an AIRE score ≥1 at their 2- and 6- week follow-up appointments.

Table 3. 10 Follow-up abdominal wound assessment (AIRE score)				
		Conventional diathermy	**PEAK PlasmaBlade™**	**p-value**
Week 2	**Total number of patients**	52	55	
	Patients with AIRE score ≥1	21.2%	20%	0.96†
Week 6	**Total number of patients**	50	55	
	Patients with AIRE score ≥1	6.0%	9.0%	0.58†
	†Mann-Whitney U Test ; AIRE: Acute Inflammatory Response Evaluation			

During the follow-up appointments, the total AIRE scores were low, not showing any statistically significant differences between the two groups. Neither was there a difference between the individual aspects of the score (erythema, oedema, pain, temperature).

3.7 Mobility

Table 3.11 shows the median number of steps from days 1 till day 7 of the admission for the two different groups.

Table 3. 11 Mobility	**Conventional diathermy**	**PEAK PlasmaBlade™**	**p-value**
Steps day 1†	n=38 0 (0)	n=44 0 (0)	0.46
Steps day 2†	n=39 92.0 (15.0 – 317.0)	n=47 150.0 (26.0 – 293.0)	0.38
Steps day 3†	n=43 389.0 (126.0 – 626.0)	n=47 400.0 (222.0 – 648.0)	0.99
Steps day 4†	n=46 717.0 (298.3 – 1173.5)	n=48 618.5 (287.8 – 1004.8)	0.84
Steps day 5†	n=35 663.0 (262.0 – 1370.0)	n=39 805.0 (309.0 – 1632.0)	0.50
Steps day 6†	n=22 635.0 (277.3 – 1019.0)	n=24 809.5 (354.3 – 1459.5)	0.17
Steps day 7†	n=9 707.0 (342.5 – 1719.5)	n=10 609.0 (218.0 – 1545.0)	0.60
†Median (IQR); Mann-Whitney U Test, n= total number of patients in group			

There was no statistically significant difference in activity (number of steps a day) comparing the different days between the two different groups.

3.8 Seroma on abdominal ultrasound scan

During their clinic follow-up appointments at 2- and 6 weeks post-operative an abdominal ultrasound was performed to evaluate the abdomen for fluid collections (seromas). In eleven patients, the abdominal drain was still *in situ* at the 2-week appointment and subsequently removed. Two patients were unable to attend the 2-week follow-up appointment, three patients were unable to attend the 6-week follow-up appointment.

Table 3.12 and 3.13 displays the results of the ultrasounds.

Table 3. 12 Seroma on abdominal ultrasound scan 2 weeks post-operative

		Conventional diathermy (n=51)	PEAK PlasmaBlade™ (n=55)	p-value
2 weeks	**Drain still *in situ***	7.8%	12.7%	1.0[Δ]
	Presence of seroma	70.6%	54.5%	0.09[∂]
	Largest seroma collection (cm^3) †	51.5 (22.0 – 95.7)	41.8 (15.0 – 73.4)	0.03
	Total seroma collections (cm^3) †	62.8 (22.0 – 110.0)	45.6 (16.8 – 98.0)	0.04

†Median (IQR); Mann-Whitney U Test; [∂] Pearson Chi-Square test; [Δ] Fisher's Exact test

Table 3. 13 Seroma on abdominal ultrasound scan 6 weeks post-operative

		Conventional diathermy (n=50)	PEAK PlasmaBlade™ (n=55)	p-value
6 weeks	**Presence of seroma**	26.0%	23.2%	0.78[∂]
	Largest seroma collection (cm^3) †	16.1 (11.6 –115.8)	19.3 (12.9 – 37.6)	0.98
	Total seroma collections (cm^3) †	16.5 (11.6 – 115.8)	22.1 (12.9 – 43.4)	0.94

†Median (IQR); Mann-Whitney U Test; [∂] Pearson Chi-Square test; [Δ] Fisher's Exact test

There was a trend towards fewer seromas at the 2-week follow-up appointment (70.6% vs 54.5%, p=0.09), but this did not reach statistical significance. At the 2-week follow-up appointment the total seroma size (cm^3) was significantly smaller in the PEAK PlasmaBlade™ group compared to the normal diathermy group (62.8cm^3 vs 45.6cm^3, p=0.04). At the 6-week follow-up appointment there were no statistically significant differences in presence and size of seromas between the two groups.

3.9 Complications

The number and type of complication experienced with the required intervention are shown in table 3.14.

Table 3. 14 Complications	Intervention	Conventional diathermy (n=52)	PEAK PlasmaBlade™ (n=56)	p-value
Free flap problem	Theatre	6	3	0.31$^{\Delta}$
Abdominal haematoma	Conservative	1	0	0.23$^{\Delta}$
	Theatre	1	0	
Abdominal seroma causing discomfort	Needle aspiration	2	2	1.00$^{\Delta}$
Abdominal seroma causing wound breakdown	Theatre	1	1	1.00$^{\Delta}$
Abdominal wound infection	Oral antibiotics	0	2	0.50$^{\Delta}$
Partial abdominal wound breakdown	Wound dressings	4	5	1.00$^{\Delta}$
Total amount of complications		15	13	0.58$^{\partial}$

$^{\Delta}$ Fisher's Exact test ; $^{\partial}$ Pearson Chi-Square test

There was a total of 28 complications in our study population, with 15 complications in the normal diathermy and 13 complications in the PEAK PlasmaBlade™ group. The complications were evenly distributed between the two groups, not showing any statistically significant differences for any of the individual complications, nor for the total amount of complications (p=0.58).

3.10 Regression analysis

To look at predictors and to identify possible confounders, regression analysis was performed.

3.10.1 Analysis of days drains were required (Cox proportional hazards model)

Comparing the machine used, the hazards ratio for the number of days drains were required was 1.16 (95% confidence interval 0.76 - 1.76; table 3.15), which did not reach statistical significance (p=0.50). Other factors such as age, BMI, flap weight, consultant, procedure and adjuvant therapies were analysed for their association with time to drain removal. BMI and

flap weight were statistically significantly inversely associated with time to drain removal; other variables were not significantly associated with the time of drain removal (Table 3.15).

Table 3. 15 Univariable Cox regression analysis for drain requirement

	Hazard Ratio	Confidence interval	p-value
Machine (Ref group: diathermy)	1.16	0.76 – 1.76	0.50◊
Age (per 5 years increment)	0.94	0.86 – 1.03	0.21◊
BMI (per 5kg/m^2 increment)	0.78	0.62 – 0.99	0.04◊
Flap weight (per 100g increment)	0.94	0.89 – 0.99	0.03◊
Consultant (Ref group: VR)	0.86	0.53 – 1.40	0.55◊
Procedure (Ref group: DIEP)	1.69	0.73 – 3.90	0.22◊
Radiotherapy (Ref group: no radiotherapy)	0.99	0.62 – 1.58	0.97◊
Neo-adjuvant chemotherapy (Ref group: no chemotherapy)	1.03	0.63 – 1.68	0.92◊
Hormonal therapy (Ref group: no hormonal therapy)	0.98	0.63 – 1.56	0.95◊

◊ Cox Model

Three multivariable analyses were conducted. In the first analysis, machine use was adjusted for the significant value BMI. In the second analysis, machine use was adjusted for the other significant variable, flap weight. In the third multivariable analysis, machine use was adjusted for both BMI and flap weight (Table 3.16).

Table 3. 16 Multivariable Cox regression analysis

	Multivariable 1	Multivariable 2	Multivariable 3
Machine (Ref group: diathermy)	1.15* (0.76 – 1.75)† p = 0.50◊	1.06* (0.69 – 1.62)† p = 0.79◊	1.08* (0.70 – 1.66) † p = 0.72◊

*Hazard Ratio (HR); †95.0% Confidence Interval (CI); ◊p-value Cox model
Multivariable 1: only adjusted for BMI (p=0.04)
Multivariable 2: only adjusted for flap weight (p=0.03)
Multivariable 3: adjusted for BMI and flap weight

After correction for significant predictors associated with drain removal, the type of machine used was not significantly associated with the length of drain requirement.

3.10.2 Logistic regression for seroma presence on 2- and 6-week ultrasound

A logistic regression was performed for the presence of seroma on ultrasound at 2- and 6-week follow-up appointments, to review the influence of different parameters. The odds ratio of 0.5 (95% confidence interval 0.22 – 1.12) for the machine's association with seroma incidence at the 2-week ultrasound almost reached statistical significance (p=0.09) (Table 3.17). At the 6-week ultrasound the odds ratio of 0.79 (95% confidence interval 0.32 – 1.95) for the machine's association with seroma incidence did not reach statistical significance (p=0.62) (Table 3.18).

Table 3. 17 Univariable logistic regression for seroma presence on ultrasound at 2 weeks

	Odds Ratio	Confidence interval	p-value
Machine (Ref group: diathermy)	0.50	0.22 – 1.12	0.09◊
Age (per 5-year increment)	1.22	0.999 – 1.50	0.051◊
BMI (per 5kg/m^2 increment)	1.26	0.80 – 1.99	0.32◊
Flap weight (per 100g increment)	1.09	0.97 – 1.22	0.16◊
Consultant (Ref group: VR)	0.44	0.19 – 1.04	0.06◊
Procedure (Ref group: DIEP)	1.70	0.33 – 8.9	0.53◊
Radiotherapy (Ref group: no radiotherapy)	1.15	0.48 – 2.74	0.76◊
Neo-adjuvant chemotherapy (Ref group: no chemotherapy)	0.88	0.35 – 2.21	0.79◊
Hormone therapy (Ref group: no hormonal therapy)	0.72	0.30 – 1.71	0.46◊

◊ Logistic regression model

Table 3. 18 Univariable logistic regression for seroma presence on ultrasound at 6 weeks

	Odds Ratio	Confidence interval	p-value
Machine (Ref group: diathermy)	0.79	0.32 – 1.95	0.62◊
Age (per 5-year increment)	1.41	1.11 – 1.79	0.005◊
BMI (per 5kg/m^2 increment)	1.17	0.72 – 1.90	0.52◊
Flap weight (per 100g increment)	1.07	0.95 – 1.21	0.24◊
Consultant (Ref group: VR)	0.24	0.07 – 0.87	0.03◊
Procedure (Ref group: DIEP)	3.5	0.66 – 18.57	0.14◊
Radiotherapy (Ref group: no radiotherapy)	0.74	0.26 – 2.07	0.56◊
Neo-adjuvant chemotherapy (Ref group: no chemotherapy)	0.80	0.27 – 2.43	0.70◊
Hormone therapy (Ref group: no hormonal therapy)	1.03	0.38 – 2.79	0.96◊

◊ Logistic regression model

Univariable logistic regression for the 2-week seroma presence did not show any significant parameters, therefore age and consultant both with a p value <0.10 were used in the multivariable logistic regression (Table 3.19).

Univariable logistic regression for the 6-week seroma presence did show a significant odds ratio for age (p=0.005) and consultant (p=0.03). Both values were used in the multivariable logistic regression (Table 3.20).

Table 3. 19 Multivariable logistic regression for seroma presence on USS at 2 weeks

	Multivariable 1	Multivariable 2	Multivariable 3
Machine (Ref group: diathermy)	0.53* (0.23 – 1.20)† p = 0.13◊	0.47* (0.21 – 1.07)† p = 0.07◊	0.49* (0.21 – 1.13)† p = 0.09◊

*Odds Ratio (OR); †95.0% Confidence Interval (CI); ◊Logistic regression model
Multivariable 1: only adjusted for age (p=0.051)
Multivariable 2: only adjusted for consultant (p=0.06)
Multivariable 3: adjusted for both age and consultant

Table 3. 20 Multivariable logistic regression for seroma presence on USS at 6 weeks

	Multivariable 1	Multivariable 2	Multivariable 3
Machine (Ref group: diathermy)	0.88* (0.34 – 2.25)† p = 0.79◊	0.76* (0.30 – 1.91)† p = 0.56◊	0.86* (0.33 – 2.26)† p = 0.76◊

*Odds Ratio (OR); †95.0% Confidence Interval (CI); ◊Logistic regression model
Multivariable 1: only adjusted for age (p=0.005)
Multivariable 2: only adjusted for consultant (p=0.03)
Multivariable 3: adjusted for both age and consultant

After multivariable logistic regression adjusting for age and consultant, the type of machine used was not significantly associated with the presence of a seroma collection at the 2-week ultrasound (Table 3.19). The same was shown in the multivariable logistic regression for the 6-week ultrasound (Table 3.20).

3.10.3 Logistic regression for complications

A logistic regression was performed for all the experienced complications. The number of complications experienced by each patient ranged from 0 to 3. Results from univariable analysis are displayed in Table 3.21.

Table 3. 21 Univariable logistic regression for complications

	Odds Ratio	Confidence interval	p-value
Machine (Ref group: diathermy)	0.73	0.29 – 1.87	0.52◊
Age (per 5 years increment)	1.10	0.88 – 1.37	0.42◊
BMI (per 5kg/m^2 increment)	1.74	1.01 – 2.98	0.045◊
Flap weight (per 100g increment)	1.11	0.98 – 1.26	0.09◊
Consultant (Ref group: VR)	0.56	0.21 – 1.46	0.24◊
Procedure (Ref group: DIEP)	1.85	0.33 – 10.37	0.48◊
Radiotherapy (Ref group: no radiotherapy)	0.84	0.31 – 2.30	0.73◊
Neo-adjuvant chemotherapy (Ref group: no chemotherapy)	2.24	0.61 – 8.29	0.23◊
Hormonal therapy (Ref group: no hormonal therapy)	0.84	0.31 – 2.31	0.74◊

◊ Logistic regression model

A higher BMI was associated with a higher number of complications, reaching statistical significance (p=0.045). Other values (age, flap weight, procedure and neo-adjuvant chemotherapy) had an odds ratio above 1, but did not reached statistical significance.

Two multivariable analyses were conducted. The first analysis adjusted for BMI only, as this was the only statistically significant predictor for complications in the univariate analysis. The second analysis adjusted for all variables with a p-value smaller than 0.10 (BMI and flap weight, Table 3.22).

Table 3. 22 Multivariable logistic regression for complications

	Multivariable 1	**Multivariable 2**
Machine (Ref group: diathermy)	0.83* (0.32 – 2.16)† p = 0.70◊	0.86* (0.33 – 2.26)† p = 0.77◊

*Odds Ratio (OR); †95.0% Confidence Interval (CI); ◊p-value ordered logistic regression model
Multivariable 1: only adjusted for BMI
Multivariable 2: adjusted for BMI and flap weight (all p<0.2)

After correction for predictors for complications, the type of machine used was not significantly associated with a higher number of complications.

CHAPTER 4: DISCUSSION

In this final discussion chapter of the thesis a comprehensive discussion on the different aspects of the research will be given. This has enabled me to critically evaluate the work I have done and draw evidence-based conclusions from my own findings and those published by others.

4.1 The primary outcome value

This study has been unable to reject the null hypothesis, as there was no statistically significant difference for the drain requirement between patients operated with the PEAK PlasmaBlade™ compared to the conventional diathermy. The conventional diathermy group required the drains for a median of 6.0 days with an interquartile range of 5.0 – 8.8 days compared to a median of 5.0 with an interquartile range of 5.0 – 8.5 days in the PEAK PlasmaBlade™ group.

In 19 patients the last drain was removed too early (draining >30mL/24 hours). Exclusion of this cohort did not result in a statistically significant difference in the amount of days the drains were required between the two groups. With a median of 6.0 days with an interquartile range of 5.0 – 9.0 days in the conventional diathermy group compared to a median of 5.0 days with an interquartile range of 4.0 – 8.0 days in the PEAK PlasmaBlade™ group. Exclusion of these cases reduced the sample size significantly. To try and overcome this imputation was applied. After imputation, in which incorrect drain removal days were replaced by expected days of drain requirement, no statistically significant difference was found.

Analysis of each of these three data sets had its own problem. The first option in which all data are included, wrongfully removed drain data will skew the actual result. When looking at the wrongful drain removed group more specifically it shows for the conventional diathermy group n=10, median=4.5 IQR 3.75 – 6.25 compared to the PPB group n=9, median=5.0 IQR 3 – 6.5. Those values are fairly similar, not showing any statistically significant difference using

the Mann-Whitney U test p=0.26. When comparing the data, the median values stay the same for both machine groups (PPB median 5.0 IQR 5.0 – 8.5 vs median 5.0 IQR 4.0 – 8.0 and CD median 6.0 IQR 5.0 – 8.8 vs median 6.0 IQR 5.0 – 9.0).

Excluding the incorrectly removed drain data as mentioned before results in a significant loss of data, resulting in the study being insufficiently powered. The problem with the imputation technique on a high percentage (17.6%) of a relatively small dataset is that it is an artificial way to increase your power and is usually not performed on the outcome of interest. Neither of the three techniques resulted in a statistically significant difference.

The Kaplan-Meier survival curve most likely makes optimal use of the existing data by including the patients whose drain was removed too early as censored data.

Looking at the Kaplan-Meier curve (diagram 1.3), the line of drain removal for the PEAK PlasmaBlade™ group lies below the conventional diathermy group at all time, but this did not reach statistical significance using the Log Rank test, p=0.42. On the contrary to the situation in which the curves would have crossed, this might suggest that the non-significant finding could have been a power issue.

Cox linear regression did identify BMI and flap weight as parameters significantly inversely associated with the time to drain removal but a multivariable analysis including those factors with machine used, did not result in a statistically significant hazard ratio.

A possible explanation for the inability to find a significant difference between the two groups can be the used power settings and mode for the PEAK PlasmaBlade™. When comparing the experimental studies in chapter 1.5.5.1 to the clinical studies in chapter 1.6, it reveals the PEAK PlasmaBlade™ was used at much lower energy settings (3) and only in the cut mode in the experimental studies compared to both cut (1 to 7) and coagulation mode (3 to 8) in the clinical studies. The largest difference in operating temperature between the two different machines, resulting in thermal collateral damage is when used in the cut mode on low power

levels. For the raise of the abdominal flap “cut” was used to dissect and “coagulation” for haemostasis, resulting in a combination of both the cut and coagulation mode. It is impossible, for either of the two machines to exactly quantify how often it was used in either of the two different settings. The use of both modes might be a factor contributing to a smaller difference than expected. For this study the settings cut 7 (35 Watt) and coagulation 7 (35 Watt) were used. Possibly these settings were too high and therefore did not result in a significant difference. It would be valuable to evaluate the PPB in a similar model but at lower power settings.

Other studies producing similar results were Ruidiaz et al. (2011) who didn’t find a difference in time to drain removal time in 20 abdominoplasties; Chiappa et al. (2018) who did not find a significant difference in drainage duration in 60 breast cancer patients; Sowa et al. (2018) who didn’t find a difference in drain requirement in 44 LD patients and Schlosshauer et al. (2019) who didn’t find a difference in drainage duration in upper arm or medial thigh lifts. The paper published by Dogan et al. (2013) was the only one that did find a reduced drain requirement after the use of the PPB compared to conventional electrosurgery in 46 mastectomy patients.

The difference in surgical area and tissue characteristics (skin in breast surgery and subcutaneous fat in abdominal surgery) could be a possible reason for the different effects of the PEAK PlasmaBlade™ on drain requirement between Dogan’s breast study (2013) and our abdominal study. The permittivity of skin (ϵ_{skin}=1832.8) is much higher compared to subcutaneous fat (ϵ_{fat}=27.22), therefore skin polarises much easier making it less resistive to an electric flux, reducing the height of heat conversion at similar power settings. Electric conductivity for skin (σ_{skin}=0.22) is also much larger than that of fat (σ_{fat}=0.025), making skin more capable of dispersing heat (Jimenez-Lozano et al., 2012).

The difference between the two breast studies (Chiappa 2018 and Dogan 2013) could be due to power settings which cannot be confirmed as Chiappa did not disclose theirs. The study population of Chiappa at al. also included quadrantectomies which result in lower wound

drainage as the wounds are much smaller and the created cavity can be closed off with sutures, therefore usually not requiring a drain.

4.2 The secondary outcome values

4.2.1 Peri-operative data

Time to raise flap

The operative time for the PEAK PlasmaBlade™ (120 min IQR 93.5 – 154.5), did not differ significantly from the conventional diathermy (129 min IQR 90 – 159.3). This shows the use of the new technology of the PEAK PlasmaBlade™ only requires a short learning curve and is as effective for dissection and haemostasis as the conventional diathermy. This is important as theatre time is expensive with an average cost of approximately £1200 per hour (Fletcher, Edwards, Tolchard, Baker, & Berstock, 2017). The senior plastic surgeons (VR and MG) performing the flap raises had the subjective perception the PEAK PlasmaBlade™ was slower/ less effective in performing haemostasis in the coagulation mode, but this was proven only subjective by the equal objective flap raise times, number of vessel clips used and post-operative haematomas recorded.

Similar results have been published in other papers comparing the operating time between the conventional diathermy and PEAK PlasmaBlade™: Duscher et al. (2019) did not find a statistical significant difference in operating time for abdominoplasties, Sowa et al. (2018) not in LD breast reconstruction operations, Dogan et al (2013) not for mastectomies and Chiappa et al. (2018) not for breast cancer surgery (mastectomy and lumpectomy). The PEAK PlasmaBlade™ has been shown to significantly reduce operating time in replacement of implantable devices such as cardiac pacemakers/ defibrillators and neuromodulation implants (Kypta et al., 2018; Kypta et al., 2015; Ughratdar et al., 2018) as the lower operating temperature makes it acceptable to touch the device leads without causing damage, making removal of the old generator out of the fibrotic tissue easier, quicker and safer. Zientara et al.

(2018) report a significantly longer operating time (5.1 minutes longer, p=0.01) in the PEAK PlasmaBlade™ group for internal thoracic artery harvest for cardiac by-pass surgery. This could be explained by the low settings at which the PEAK PlasmaBlade™ was used, namely cut mode 1 and coagulation mode 5. Due to the reduced haemostatic ability of the PPB on those low settings a modification to the preparation technique was introduced, namely clipping of the distal end of side branches. Duscher at al. (2019) was the only other clinical study using the PPB on a low setting 3 (not specified if this was cut or coagulation) but this did not result in an increased operating time as mentioned earlier.

Flap weight

Despite randomisation, the flap weight was significantly (p=0.03) higher in the conventional diathermy group 958.5 gram (IQR 759 – 1239) compared to the PPB group 833.0 gram (IQR 575.0 – 1031.0). Therefore flap weight is a confounding factor in this study for which should be corrected to prevent false associations. Univariate Cox regression analysis was used to identified flap weight as a significant (p=0.03) covariant with a hazard ratio of 0.94 per 100 gram increment. Multivariable Cox regression was performed to correct for the signififcant flap weight on the primary outcome value. After correction with the multivariable Cox regression the effect of the different machines on the primary outcome value (days drain requirement) remained insignificant.

4.2.2 Inflammatory cytokines

Ozdogan et al. (2008) and Yilmaz et al. (2011) showed a significant difference in levels of TNF-alpha and IL-6 in 24-hour post mastectomy drain fluid, between knife and electrosurgical dissection. These were the only two studies published comparing cytokine levels after scalpel and electrosurgery. As mentioned in the introduction the reported fluid collection within 24 hours post-operatively was the major flaw in the second paper.

This RCT was unable to find a significant difference in inflammatory cytokines on day 0,1 and 2 between the two groups. There were some observed tendencies for MIP-1 beta on day 0

(p=0.07), MIP-1 alpha on day 1 (p=0.054) and IL-18 on day 2 (p=0.07) towards statistically significant lower values in the PEAK PlasmaBlade™ group. Clinical significance of these values is unclear and further research on the effects of electrosurgery on inflammatory cytokines is required. As the power of this study was not calculated for the levels of inflammatory cytokines, the inability to reach statistical significance could be due to a too small study population. A possible explanation for the failure to show a significant difference in key inflammatory markers between the two different machines could be because both use electricity, which causes collateral thermal injury. This finding also supports the hypothesis that if the PEAK PlasmaBlade™ is used in both the "cut" and "coagulation" mode at higher settings, its' operating temperature rises, resulting in more collateral tissue damage comparable to the conventional diathermy.

When reviewing Table 2.4 there is a clear difference between the LDD and LLOQ between the 2017 and 2018 measurements for most cytokines. The laboratory has confirmed these differences are not caused by the calibration of the machines used for the analysis. In hindsight analysis of all the samples at the end of the study would have been more preferable. The reason for the first analysis half way through the study was to identify any possible problems with the sample collection, storage or transport on dry ice to the United States, giving us the opportunity to make adjustments, would it have been required, at least ensuring correct sample testing for half of the included patients.

4.2.3 Pain scores

The numerical rating scale (NRS) from 0 to 10 was a useful tool to assess pain intensity during the inpatient stay. It's easy use, feasibility and good compliance have been proven in previous studies (Haefeli & Elfering, 2006). Other scores such as visual analogue scale (VAS) or graphic rating scale (GRS) were deemed less useful as scoring is more time consuming, more vulnerable to measurement errors and more susceptible to misinterpretation (Haefeli & Elfering, 2006).

In the immediate post-operative period in recovery pain was significantly higher in the PEAK PlasmaBlade™ group. A possible explanation for the significantly higher pain in the PPB group could be correlated to the significantly lower flap weight in this group. In patient with a smaller amount of abdominal fat a larger abdominal flap including more tissue would have to be harvested to acquire a sufficient volume to reconstruct the breast. This would result in a tighter more painful abdominal closure. Another factor most likely having influence on pain immediately post-operatively is the axillary lymph node clearance, which is removal of all lymph nodes from the armpit. Axillary lymph node clearance was performed in 32,1% of the PEAK PlasmaBlade™ group and 21.2% in the conventional diathermy group, but this did not reach statistical significance. Possibly the difference in pain score is based on interpatient variability as pain remains a subjective matter.

Spektor et al. (2016) publishes a paper in 2016 comparing pain and analgesia requirement in a prospective, non-randomised, non-blinded cohort study including 100 patients aged 3 to 12 years undergoing a tonsillectomy performed with the PEAK PlasmaBlade™ or bipolar radiofrequency ablation (coblation). Parents or legal guardians had to quantify pain in the first 14-days post-operative using a validated 11-point proxy-evaluated paediatric pain scale (Children's and Infants' Postoperative Pain Scale, CHIPPS) over the phone. A mean pain difference of 3 points was considered clinically relevant. The requirement for any doses of narcotic or non-narcotic medication were also registered. Pain scores were significantly lower in the PEAK PlasmaBlade™ group between post-operative days 7 to 9, but this did not reach the clinically significant difference of 3. There was no significant difference in the amount of analgesic medication required between the two groups. Drawbacks of the study were the young age of the patients, requiring a proxy to rate the pain, the pain assessment over the phone and the non-blinded/ non-randomised character of the study.

More recently Tan et al. (2019) published their study comparing the PEAK PlasmaBlade™ to monopolar electrocautery for tonsillectomy in a prospective double-blinded randomised controlled trial in 58 adults. They found that patients in the PEAK PlasmaBlade™ groups were able to pain-free swallowing in a shorter period of time compared to the electrocautery group

(13.28 vs 15.76 days p=0.035). There was no difference in the daily visual analogue score for pain nor in the number of analgesia tablets taken. Patients who underwent their tonsillectomy with the PEAK PlasmaBlade™ had a higher satisfaction score compared to those who underwent the procedure with the monopolar electrocautery (8.92 vs 8.24 out of 10, p=0.046). This study has been unable to show a reduction in pain after use of the PEAK PlasmaBlade™ possibly as other factors such axillar node clearance, inter-rib dissection for vessel preparation, drains and tension on abdominal closure are more significant in the amount of pain experienced, compared to the abdominal wound surface created. The significant difference on day 0 in pain scores will most likely be caused by other confounding factors and not the difference in machine used.

4.2.4 Mobility

Mobility was equal between the two groups during the in-patient period not showing any statistical significance. This variable was measured not because a difference was expected but to make sure both groups were mobilising equally because immobility has been linked to a reduced drain out-put (Beer & Wallner, 2010).

4.2.5 Abdominal wound assessment (AIRE scores)

Both during the in-patient and out-patient period the AIRE scores (total and individual aspects) have not shown a statistically significant difference in local inflammatory reaction of scars between the PEAK PlasmaBlade™ and conventional diathermy group. During admission (day 1 to day 7) total AIRE scores were low in both groups, which was expected as the inflammatory reaction of wound healing requires time to develop.

At the 2-week appointment most patient had an AIRE score of 0 (78.7%, n=85), the rest had score of 1 (13.9%, n=15) and 2 (3.7%, n=4). The highest AIRE scores acquired were 5 (0.9%, n=1) and 6 (1.9%, n=2). At the 6-week appointment most patients had an AIRE score of 0 (89.8%, n=97), the rest had scores of 1 (2.8%, n=3), 2 (2.8%, n=3) and 4 (0.9%, n=1). The

highest score acquired by one patient (0.9%) was 9. As skin incisions were made with a scalpel in both groups, a difference in this AIRE score was not expected.

Richter et al. (2012) introduced the AIRE score for local inflammatory reactions of scars to compare two different methods of skin closure. They did show some significant differences of individual aspects of the score but were unable to show significant differences for the total AIRE scores at 24 hours, 7 days, between 12 to 25 days, 90 days, 6 months and 12 months. The AIRE scoring system has only been used in the publication by Richter et al. (2012). The paper does not comment on validity, reproducibility, sensitivity and inter-rater reliability of their scoring system. In our study the abdominal wounds were scored by one person, the research fellow, therefore only influenced by intra-rater reliability.

A great variety of scar-measuring devices and assessment scales have been published over the years, rating both objective and subjective aspects of scars. Validation processes have demonstrated acceptable consistency and reliability, but due to evaluation of only a few aspects they have limited sensitivity. This results in the ability to only detect large differences between scars. Most studies on classifications and scar evaluation focus on burn scars, making them less applicable to (early) surgical scars (Fearmonti, Bond, Erdmann, & Levinson, 2010).

4.2.6 Total abdominal drain fluid output

This study has been unable to show a statistically significant reduction in the total drain output after performing the abdominal flap raise with the PEAK PlasmaBlade™. The influence of electrosurgery on abdominal seromas in the literature is contradictory and mainly focussed on (cosmetic) abdominoplasties. Even though there are a lot of similarities between the cosmetic abdominoplasty and DIEP/MS-TRAM donor site there are usually differences in placement of scar, amount of intramuscular dissection, operating time, BMI and dissection technique (Salgarello et al., 2012). An RCT performed by Mash et al. (2015) comparing scalpel and handheld electrocautery dissection in abdominoplasties in 102 patients did not show a difference in seroma rates. Rousseau et al. (2011) published in 2011 a longer drainage period,

higher drain volumes and more seroma collections after an abdominoplasty (n=551) with diathermo-coagulation compared to scalpel dissection. In 2015 similar results were reported by Valença-Filipe et al. (2015) in 119 abdominoplasties. All studies suffered from design flaws introducing a high chance of bias.

In clinical studies comparing the PPB to electrosurgery Chiappa et al. (2018) in 60 breast cancer patients and Duscher et al. (2019) in 57 abdominoplasty patients also did not find a significant difference in total abdominal drain output. In contrast to Dogan et al. (2013) in 46 mastectomy patients, Sowa et al. (2018) in 44 LD patients and Schlosshauer et al. (2019) in 24 upper arm and medial thigh lifts, who did find a significant reduction in total drainage after the use of the PPB.

Abdominal drain fluid contains both blood and wound fluid and usually changes from serosanguinous initially to serous after a few days. A reduction in total drain fluid can therefore also be caused by a reduction in immediate post-operative bleeding. Schlosshauer et al. (2019) were the only group that tried to control for this by also reporting the drain output for the 1st post-operative day. A possible explanation for the difference found in total drainage in the paper from Schlosshauer et al. were the extremely high settings used for the conventional diathermy (Coagulation max. 80 Watt and cut max. 180 Watt). Sowa et al. did not disclose their power settings, therefore this could also be an explanation for their significant difference.

4.2.7 Complications

Haematoma and wound healing problems

Abdominal haematomas were experienced twice in the conventional diathermy groupcompared to none in the PEAK PlasmaBlade™ group. This did not reach statistical significance. These results support the conclusion that the PEAK PlasmaBlade™ is as effective in haemostasis as the conventional diathermy.

Minor wound healing problems occurred in about 1% of cases, which all resolved with wound dressing. No significant differences were seen in wound healing.

Univariate logistic regression for complications showed a statistically significant association with a higher BMI. Correction with multivariable logistic regression, the type of machine was not significantly associated with a higher number of complications.

Due to the low number of experienced complications in both groups we have been unable to show statistically significant differences. These findings are comparable to papers published by Dogan et al. (2013), Chiappa et al. (2018), Kypta et al. (2018) and Duscher et al. (2019), who were also unable to show statistically significant differences in complications in their clinical studies comparing the PPB to the conventional diathermy.

Post-operative seroma collections

Only two patients required surgery for abdominal wound breakdown caused by excessive seroma production and four required a single needle aspiration for a large seroma causing discomfort. These complications were equal between the two groups and did not reach statistical significance.

At the two-week follow-up appointment there was a tendancy towards more seromas in the conventional diathermy group, almost reaching statistically significance (p=0.09). Seroma collections were statistical significantly smaller (p=0.04) in the PEAK PlasmaBlade™ group. Five patients developed a new seroma collection between the 2- and 6-week appointment, two of them had the abdominal drain only removed at the 2-week follow-up appointment. In most patients (n=42, 64%), the one or multiple seroma collections at 2 weeks had spontaneously reabsorbed at the 6-week appointment.

These findings are similar to Di Martino et al. (2015) who evaluated the beginning and progression of seroma formation following abdominoplasty in a prospective trial by performing abdominal ultrasounds at 7-day intervals in 21 female patients. They concluded the highest incidence of seroma formation was between day 11 (38.1%) and 18 (33.3%) post-operatively, which fell significantly to 19% on day 32.

The tendancy towards less abdominal seromas after the use of the PEAK PlasmaBlade™ at the 2-week follow-up appointment might have resulted in a significant difference if a larger patient population would have been included as this study was not powered for seroma occurrence.

The follow-up for this study was only 6 weeks, but patients were seen as part of their regular follow-up at 6 months and 1 year post-operatively. In this time one patient presented 3 months post-op with a chronic seroma, not requiring any further intervention. Potentially more patients will have developed subclinical small chronic seromas with pseudo-cyst formation without causing any discomfort or influencing cosmetic outcome possibly due to a high BMI of 28. Further studies with long-term follow-up using abdominal ultrasound could give more clarity on this subject, though clinical relevance is questionable. The low incidence (0.3%) for surgical intervention for late seromas in TRAM and DIEP flaps patients has also published by Nahabedian (2007).

As drainage of every seroma collection is unnecessarily invasive and increases the risk of infection, in this study only large seromas causing discomfort to the patient were drained via needle aspiration. Therefore, an alternative method to estimate the volume of an identified seroma collection had to be used. With the use of the ultrasound machine the dimensions (length, width and maximum height in cm) of each seroma collection were measured. Since the shape of an abdominal seroma collection most approximates the shape of half an ellipsoid its formula was used to estimate the volume. This method most likely underestimates the actual volume of a seroma collection, but because ultrasound was performed by a single person using the same technique for every individual measurement, outcomes were considered comparable.

Logistic regression did identify age and consultant as statistically significant parameters for the presence of seroma at 6 weeks. Correction for those in a multivariable logistic regression for seroma presence at 6 weeks, did not result in a significant odds ratio for the machine used.

The definition for seroma greatly varied between the different clinical papers, making it difficult to compare results. Seromas were usually only identified clinically which also leads to under diagnosis of this complication.

4.3 Experienced difficulties

The Post Graduate Medical Institute Clinical Trials Unit (PGMICTU) at the Anglia Ruskin University set-up an online electronic database (MACRO database) for the data collection. A print-out of the Case Report Forms (CRFs) was used to collect the data during the study period. Those results were added onto the database during the course and after completion of the study. After finalising the data entry onto the database, it was exported into SPSS .sav files. The data had to be broken down in different files as it was too large to process. The separate .sav files had to be adjusted considerably to allow data analysis with SPSS. Due to the necessity for adjustments which were very time-consuming, the usefulness of the MACRO database is questionable.

4.4 Limitations of the study

The power calculation for this randomised controlled trial was based on the data acquired from a pilot study performed in our department (Chow et al., 2019). This pilot study only included 40 MS-TRAM/DIEP breast reconstruction patients, resulting in 20 patients in the normal diathermy and 20 patients in the PEAK PlasmaBlade™ group. The mean amount of days the abdominal drains were required was calculated using the two-sample t-test. Because the power calculation was only based on a small patient population, the results could be skewed, leading to a number of patients required which is too low to show a statistically significant result.

For this study patients undergoing both the DIEP and MS-TRAM procedure were included, which could be a confounding factor. The number of included MS-TRAM flaps was low and

not significantly different between the two groups. If an MS-TRAM was clinically required only a small amount of muscle would be sacrificed, making it very comparable to the DIEP. Regression did show type of procedure was a confounding factor, but this never reached statistical significance.

Due to the high costs of the drain sample testing it was not possible to include patients requiring diversion from the study protocol. Therefore, a per-protocol analysis was performed for this trial, which could result in bias. The main reason for patient exclusion from follow-up was conversion into a bi-pedicled DIEP flap in seven cases, which was one of the exclusion criteria. A conversion from a uni-pedicled into a bi-pedicled DIEP flap is required if the abdominal fat tissue does not receive sufficient blood supply from one blood vessel. This can be difficult to judge pre-operatively and was unexpectedly required in seven patients. One patient had a large abdominal hernia, requiring repair with a mesh by the general surgeons, one surgery was cancelled, and two patients were operated by a different surgeon. All the reasons for post-randomisation exclusion were unrelated to the type of operating machine used.

Due to 1:1 randomisation of the two groups in blocks of 6, and exclusion of 11 patients after randomisation, the two groups were unequal when the predetermined number of 106 inclusions was reached. It was therefore decided to include a further two patients in the hope the power-calculated minimal sample size of 53 would be met. Unfortunately, this number was not reached resulting in the final numbers of 56 patients in the PEAK PlasmaBlade™ group and 52 in the conventional diathermy group.

To be able to include enough patients in an acceptable time period it was required to include patients from two senior plastic surgeons (VR and MG). Operating techniques of both surgeons are very similar. The standardised operation protocol reduced inter-operator variation further. Both surgeons' patients were equally divided over the two groups.

Regression analysis did show a consultant was a significant predictor for seromas at 6 weeks, therefore making it a likely confounder, for which was corrected in the multivariable regression.

The single centre character of the study could make the results less transferable to other units and is something that must be kept in mind.

The used settings for the diathermy of cut 40 Watt and coagulation 40 Watt were chosen as these are levels normally used for a standard DIEP flap raise. The PEAK PlasmaBlade™ settings of cut 7 (35 Watt) and coagulation 7 (35 Watt) were discussed with the production company Medtronic and deemed the most suitable for this type of operation. For both machines, the cut mode was used for cutting and coagulation for haemostasis. Unfortunately, it is impossible to exactly quantify the use of the different electrosurgical modes (cut/coagulation). Possibly the used machine settings for the PPB were too high to result in significantly less collateral thermal injury

4.5 Strengths of study

The randomised controlled character of this study is a strength, which will reduce selection bias (Groenwold, 2013). The randomisation was mostly successful but did result in a significantly higher resected flap weight in the conventional diathermy group. Prolonged drain requirement and increased seroma formation have been linked to a higher flap weight and is therefore a confounding factor (P. Andrades & Prado, 2007). Cox regression analysis of our data did identify flap weight as significantly inversely associated with drain requirement and therefore correcting was applied. Linear regression did not identify flap weight as a significant variable for the presence of seroma at the 2- and 6-week ultrasound, consequently it was not required to correct for this.

The double blinded character of the study is another strength as it reduces the chance of experimenter bias. I personally would never consider falsifying results but are able to imagine why researches could be tempted to do so. Despite the fact negative findings are valuable

and make an important contribution to new knowledge, they can be more difficult to publish and are not as satisfying as finding something significant. By blinding the patients, information bias was reduced because knowing the “new” machine was used could influence a patient as they think they should feel better having received the new treatment option. Values that could have been affected are the pain score, morphine use and mobility as patients would have had an influence on these three (Groenwold, 2013).

Most patients completed the 6-week follow-up, with only three patients in the conventional diathermy and one patient in the PEAK PlasmaBlade™ group not attending this final appointment. The completion of the study by 96.3% of the participants will reduce the chance of selection bias (Groenwold, 2013).

4.6 Contribution to new knowledge

This study had a well-designed study research protocol explicitly outlining data collection and analysis with a standardised operating protocol, standardised diathermy and PEAK PlasmaBlade™ settings, clear outcome values and a set follow-up period for each patient. All data was collected by one person (myself, the research fellow). No adjustments were made to the study protocol after commencement of the study. All these factors help to reduce bias and result in a higher level of evidence compared to studies previously published on the subject (Smith & Noble, 2014).

Abdominal seroma collections can be identified clinically but abdominal ultrasound is the method of choice as it is more sensitive resulting in a higher accuracy of fluid collection identification (Marcello Di Martino et al., 2010; M. Di Martino et al., 2015). Using the ultrasound machine to identify seromas in DIEP and MS-TRAM breast reconstruction patients has given more information about the natural evolution of seromas in this cohort, which can be a valuable baseline for future comparisons.

This level 1 evidence study shows the PEAK PlasmaBlade™ at settings cut-7 and coagulation-7, does not have a significant benefit over the conventional diathermy for abdominal free flap harvest, as it does not reduce drain requirement or total output and does not result in a reduction in complications. These results can also be considered for other procedures resulting in large (donor site) wounds such as latissimus dorsi breast reconstruction, cosmetic abdominoplasties and abdominal wall reconstructions.

4.7 Conclusion

Experimental studies on the use of the PEAK PlasmaBlade™ have showed very promising results, with regards to wound healing profiles and reduction in collateral thermal injury. Though clinical studies so far have mostly been unable to reveal significant improvement in post-operative recovery and a reduction in complications, possibly due small numbers and bias following poor design.

The conducted large double blinded randomised controlled trial including 108 abdominal free-flap breast reconstruction patients has been unable to show a statistically significant difference in drain requirement, total drainage or complications between patients operated with the conventional diathermy and the PEAK PlasmaBlade™ using the cut 7 and coagulation 7 settings. Inflammatory marker levels were similar between the two study groups, suggesting comparable inflammatory responses. Immediately post-operative pain scores (day 0) were significantly higher in the PEAK PlasmaBlade™ group, but most likely due to factors other than the used operating machine. The flap weight was significantly higher in the conventional diathermy group, which could have been a confounding factor, but logistic regression did not identify flap weight as a significant parameter for seroma presence at the 2- and 6-week abdominal ultrasound. There was a trend towards less seromas at the 2-week follow-up appointment, which were significantly smaller in the PEAK PlasmaBlade™ group. These differences had disappeared at the 6-week follow-up appointment, making the 2-week findings

of questionable clinical significance. Despite the high incidence of seromas on abdominal ultrasound after abdominal based autologous breast reconstruction, intervention was rarely required in either of the two groups.

In the future, further high-quality clinical trials should to be conducted for example on lower coagulation and cut settings, to give more information regarding the potential benefits of different electrosurgical devices on improving recovery time and reducing complications, all with the purpose to raise the overall care for our patients to the highest possible level.

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LIST OF APPENDICES

Appendix 1: Different settings PEAK PlasmaBlade™ with corresponding power levels

PEAK

Pure Cut

Blend

Pinpoint

Spray

Tissue Effect	Level (LCD display)	Mode	Power [W-RMS]	Maximum Output Voltage (Vp-p)	Duty Cycle (Typical, %)
CUT Low hemostasis, low collateral damage	1	Low Cut	0.5	1530	3.75
	2		2	1720	3.75
	3		6	1780	3.75
	4		10	1910	3.75
	5		20*	1990	3.75
	6	Medium Cut	20	708	100
	7		35	708	100
	8		50**	708	100
High hemostasis, higher collateral damage	9	High Cut (Blend 1)	25	1520	75
	10	High Cut (Blend 2)	50	2080	50
COAG Low hemostasis, low collateral damage	1	Low Coag	15	1290	19
	2		20	1550	19
	3		25	1690	19
	4		30	1880	19
	5		35	2020	19
	6	High Coag	30***	3960	12
	7		35	4260	12
	8		40	4520	12
	9		45	4720	12
High hemostasis, higher collateral damage	10		50	5000	12

Appendix 2: Materials and Methods cytokine analysis Myriad.

Materials and Methods

All samples were stored at less than -70°C until tested. Samples were thawed at room temperature, vortexed, spun at 3700 x g for 5 min for clarification and transferred to a master microtiter plate. Using automated pipetting, an aliquot of each sample was added to individual microsphere multiplexes of the selected Multi Analyte Profile (MAP) and blocker. This mixture was thoroughly mixed and incubated at room temperature for 1 hour. Multiplexed cocktails of biotinylated reporter antibodies were added robotically and after thorough mixing, incubated for an additional hour at room temperature. Multiplexes were labelled using an excess of streptavidin-phycoerythrin solution, thoroughly mixed and incubated for 1 hour at room temperature. The volume of each multiplexed reaction was reduced by vacuum filtration and washed 3 times. After the final wash, the volume was increased by addition of buffer for analysis using a Luminex instrument and the resulting data interpreted using proprietary software developed by Myriad RBM. For each multiplex, both calibrators and controls were included on each microtiter plate. Eight-point calibrators to form a standard curve were run in the first and last column of each plate and controls at 3 concentration levels were run in duplicate. Standard curve, control, and sample QC were performed to ensure proper assay performance. Study sample values for each of the analytes were determined using 4 and 5 parameter logistics, weighted and non-weighted curve fitting algorithms included in the data analysis package.

Appendix 3: First prize poster presentation Anglia Ruskin University Cambridge -11th Annual research study conference July 2017.

Anglia Ruskin University

Faculty of Medical Science

Improving Breast Reconstruction

Thessa Friebel

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INTRODUCTION

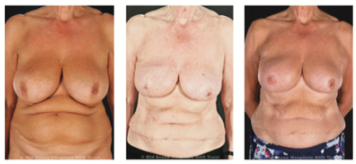
Survival 10 years 78%

BREAST CANCER

- 1 in 8 women develop breast cancer → 55,000 each year, 150 every day or 1 person every 10 min
- 57% have breast-conserving surgery and 43% have a mastectomy (operation to remove the whole breast)

BREAST RECONSTRUCTION

- Implants can be used to reconstruct the breast but may cause complications if radiotherapy is required. A more natural and durable result can be achieved with the patient's own tissue. The 'Gold Standard' for this is the Deep Inferior Epigastric Perforator (DIEP) flap consisting of the patient's abdominal skin and fat



Pre-operative | 1 yrs Post-operative | 4 yrs Post-operative

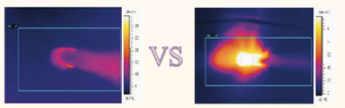
DIEP FLAP OPERATION

- 5 hour operation; 7 days in hospital; 6 week recovery
- Conventional diathermy machine used, which releases heat to cut through tissue and stop bleeding

Pre-operative markings for an delayed DIEP reconstruction | Cutting of the flap, detaching it from the abdominal wall while preserving a blood vessel perfusing the tissue | Closure of the abdomen, leave two drain tubes on the both sides | The abdominal tissue is transplanted to the breast, connecting the 3-4mm blood vessels to the chest vessels with the use of an operating microscope

PEAK PLASMA BLADE™

- Alternative equipment to cut the tissue. Introduced in 2008, produced by Medtronic
- Uses brief pulses of radiofrequency energy to induce electrical plasma along the edge of a thin 99.5% insulated electrode
- This technology enables the device to operate at significantly lower temperatures than traditional electrosurgical instruments



PEAK PlasmaBlade™: 40 - 170°C | Diathermy machine: 200 - 350°C

RESEARCH QUESTION

- Does the use of the PEAK PlasmaBlade™ in abdominal DIEP surgery lead to quicker recovery compared with the conventional diathermy machine?

▪ Less thermal injury →Less drain fluid production → Earlier drain removal (if <30ml in 24h) → Earlier discharge home

STUDY DESIGN

Patient Selection

RANDOMISED CONTROLED TRIAL
- 106 DIEP patients

DOUBLE BLINDED
- Patient and Research Fellow

INCLUSION
- Patients undergoing unilateral DIEP breast reconstruction

EXCLUSION
- Body Mass Index< 20
- Diabetes
- Smoker
- Diabetic, Heart disease, Clotting disorder
- Immunosuppressed

INFORMED CONSENT

Day 0: Randomisation and Surgery

Conventional diathermy

PEAK PlasmaBlade™

Day 1-7: Inpatient stay

ABDOMINAL DRAINS
- Amount of mL in drain bottle
- Weight of drain bottle
- Drain fluid samples → TNF-ß, IL-4, IL-6, IL-10

PAIN
- Pain score (0 – 10)
- Amount of morphine used (mg)

MOBILITY
- Amount of steps on pedometer

ABDOMINAL WOUND ASSESSMENT
- Acute inflammatory response (AIRE) score

COMPLICATIONS

Week 2 and 6: Outpatient Follow-Up

ABDOMINAL SEROMA EVALUATION
- Abdominal ultrasound

ABDOMINAL WOUND ASSESSMENT
- AIRE score

COMPLICATIONS

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