TUMESCENT INFUSION FOR SPLIT THICKNESS SKIN GRAFTING

by

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A Thesis Submitted to the Faculty of the

COLLEGE OF MEDICINE

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE
WITH A MAJOR IN MEDICAL PHARMACOLOGY
PERFUSION SCIENCES

In the Graduate College

THE UNIVERSITY OF ARIZONA

2018

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Table of Contents

List of Figures and Tables

Definitions

1. BSA – Body Surface Area
2. BUMC – Banner University Medical Center
3. BUMC-T – Banner University Medical Center - Tucson
4. STSG – Split thickness skin graft
5. FTSG – Full thickness skin graft
6. AG – Allograft
7. XG – Xenograft
8. TBSA – Total Burn Surface Area
9. MAT – Machine Aided Tumescence
10. MT – Manual Tumescence
11. IRB – Investigational Review Board
12. MD1 – Surgeon 1
13. MD2 – Surgeon2
14. OR – Operating room
15. EBL – Estimated blood loss
16. CBL – Calculated blood loss
17. BV – Blood volume
18. Hgb – Hemoglobin
19. Hct - Hematocrit

ABSTRACT

Current literature indicates a significant decrease in operative blood loss with the usage of a hemostatic agent for auto-graft sites.[11, 12] Tumescence, the localized infiltration of subcutaneous solution to prepare auto-graft donor site, builds counter pressure under the dermatome, which is a mechanical device that allows for harvest of a uniform thickness split thickness skin graft. Tumescent infusion can be done manually or by a device. The process of manual injection through a syringe is operator dependent and divides the total volume of the infusate into several aliquots, which limits delivery efficiency. Additionally, when manually injected through a syringe, limitations exists for temperature management and infusate distribution. Recently our group modified a roller pump setup for tumescent infusion upon request by our hospital's trauma and burns surgeon. A novel aspect of our setup over existing machine-operated tumescent infusion systems was the incorporation of a heat exchanger to warm the infusate. This alternative method of using Roller pump – heat exchanger device delivers a constant rate of infusate without any pauses, and simultaneously warms the infusate to assist with intra-operative thermoregulation.

After conducting a retrospective chart review for patients at Banner University Medical Center, for patients who underwent split thickness skin grafting from September 2016 to May 2017 we found that mean post-operative temperatures in the machine aided tumescence (MAT) n = 43 group with surgeon 1 (MD1) was 36.6, which represents a

mean -0.18 degree C decrease from pre-operative temperatures. Comparatively, the manual tumescence (MT) group with surgeon 2 (MD2) (n = 19) post-operative temperature was 35.6 degrees and represent a mean -1.36 degrees C change. ($p \leq 0.0001$) For calculated blood loss and transfusions, MAT/MD1 (n = 20) was found to have significantly higher blood loss and transfusion requirements than the MT/MD2 (n = 13) group with a mean of 1.1 ± 0.98 mL/cm2 and 276 ± 316 mL pRBC transfusion requirement, whereas the MT/MD2 group demonstrated a mean 0.55 ± 0.54 mL/cm2 CBL and 43.5 ± 94.3 mL pRBC transfusion requirement. ($p=0.08$) In a prospective in-vitro analysis, it was determined that mean infusion duration for 0.7 L of tumescent solution at an average infusion rate of 150 mL/min, was 1156 seconds with MT. (n=15) Comparatively MAT (n=15) accomplishes the same volume infusion in 280 seconds, which was a 76% decrease in infusion duration. ($p \leq 0.0001$)

Results indicated that infusion duration was significantly lower for MAT compared to MT. Intraoperative temperature change was significantly less for MAT/MD1 than MT/MD2. Calculated blood loss and transfusion requirements were significantly higher for MAT/MD1 compared to MT MT/MD2. Overall, infusion duration and intraoperative temperature management favored MAT/MD1, while blood loss and transfusion requirements favored MT/MD2. Negative outcomes for increased blood loss and transfusion requirements may suggest that tumescence with MAT/MD1 was not suitable for all patients. However, decreased infusion duration and superior temperature management may outweigh adverse effects in blood loss for patients that are more susceptible to clinical hypothermia.

Introduction

Trauma, burns, and infection are the leading causes that require skin grafting. Of those, the most common situation is from burn injury. In 2016, 486,000 burn injuries occurred that required medical attention. Of these, 40,000 required hospitalization, often with multiple skin graft procedures.[5] At Banner University Medical Center - Tucson, skin grafting exists across multiple departments with various techniques and outcomes. However, perfusion assisted tumescence was unique to trauma surgery. Perfusion assisted tumescence with roller pump and heat exchanger was a novel and unique method for perfusionists to help assist in STSG procedures. In September of 2016, our perfusion group at BUMC-T, under direction of the chief perfusionist and trauma surgeon, utilized a roller pump and cardioplegia circuit to aid in surgery. Normally, this equipment was meticulously managed for the cardiac suite, for precision delivery of a cardiac arresting agent.

Tumescent infusion, or tumescence is the localized subcutaneous infiltration of a solution. Tumescence can be used for excision of tissue or more commonly, to prepare autograft donor-sites. Tumescence with our method achieves an array of benefits, the three most common are: vasoconstriction, which reduces bleeding and maintains local anesthesia. Counter pressure, which assists with dermatome mediated auto-graft harvesting, and finally thermal regulation, which was not normally achieved with normal tumescence, but in our case was a novel contribution to patient temperature control.

Thermal regulation is lost after severe burns, however after about the second to third day post injury, burn victims reach a hyper metabolic state which results in fatal physiological exhaustion if not treated.[2] Much of that hyper-metabolic rate, is caused by increased heat production to replace what is lost. At BUMC-T, temperature management was under control of the anesthesia team. Management strategies include increasing ambient room temperature above 30-40 degrees Celsius or 86-104 Fahrenheit, Bair Hugger forced air warming systems, and warming blankets/pads.

Hemostasis, perioperative blood loss and transfusions are equally important concerns for skin graft surgery. Medical management of patients at BUMC-T often require multiple surgeries and have extended ICU stay due to severity of injury. As such, transfusion thresholds were kept around 7.0 grams per deciliter, whereas normal ranges for hemoglobin in males is 13.5-17.5 and 12.0-15.5 in females. [21] In addition, patients that present with burn injury often require many events of debridement and excision, which is the removal of non-viable tissue. These events often necessitates large transfusion amounts intra-operatively and post operatively in the ICU. The combination of which, was not without risk.

The most glaringly obvious complication of blood product administration was the transfusion of mismatched blood products. Complications are rare, but often fatal. Transfusion can results in coagulation abnormalities involving serum biochemistry, acid-base status, and temperature homeostasis. Other adverse effects include: hemolytic reactions, allergic reactions, circulatory overload, air embolism, hyperkalemia, citrate toxicity, transmission of infection, and graft vs host disease.[22]

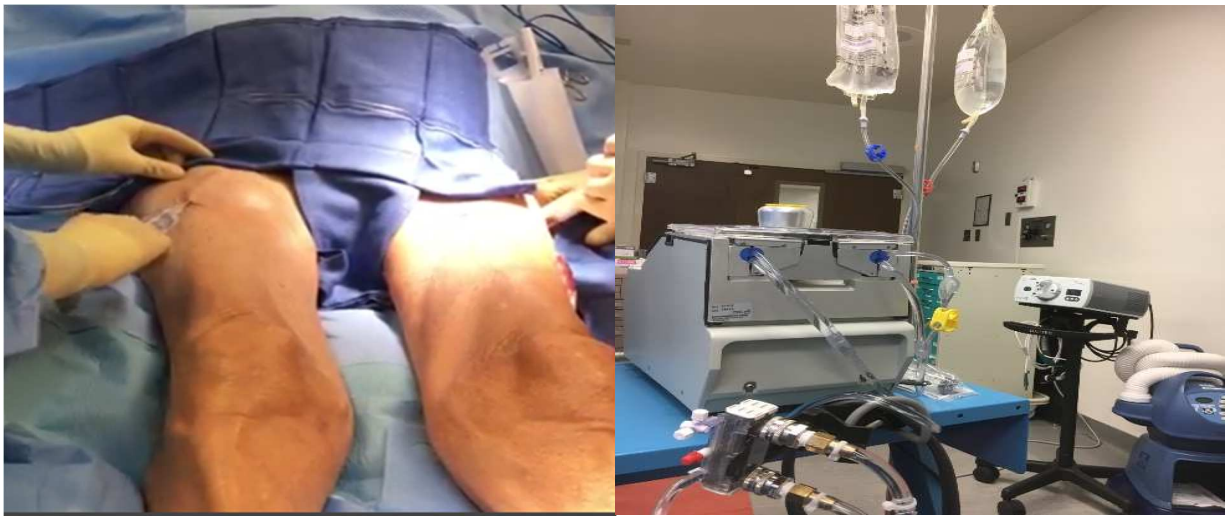


Figure 1 Methods of tumescence generation: (Left) MT method showing infusion by hand pressure with a 60 mL syringe. MAT method showing roller pump setup with tumescent solution.

Purpose

Patients undergoing split thickness skin grafting associated with burns often require prolonged operative times. Additionally, in cases of severe burns, thermal regulation of core temperature is lost.[2, 5] Tumescence creation using Roller pump – heat exchanger device is advantageous to Manual method by virtue of superior delivery efficiency and ability to warm the infusate simultaneously. Our proposed study quantifies this efficiency by measuring actual amount of time taken to deliver fixed volume of infusate with added heat function, and compare it with Manual method and hence comparing operative time/temperature management with a more efficient system.

Improving burn patient outcomes requires considerable preparation during ICU management and intra-operatively. For example, OR temperatures are generally kept above 29.4 C to maintain core temperature.[3] Burn patients have been shown to have an increased cardiac workload, myocardial oxygen consumption, and marked tachycardia. [2] The risks of physiologic exhaustion requires that the patient time in the operation room be limited. The Use of Roller pump – heat exchanger device to create tumescence at donor sites prior to autograft harvesting allows the delivery of a constant rate of infusate, hence eliminating the repeated step of refilling syringes needed in the manual method. Operative time reduction has a direct impact on operating room utilization, hospital work flow, and patient outcome.

As such, the hypothesis of our project was that: machine aided tumescence will reduce infusion times, decrease intraoperative temperature change, and reduce blood

loss/transfusion requirements, compared to manual tumescence in patients who undergo split thickness skin grafting.

Specific Aim #1:

To quantify and compare infusion time required to create tumescence between machine aided tumescence and manual tumescence, in patients who underwent split thickness skin grafting.

Specific Aim #2:

To quantify and compare intraoperative temperature changes between machine aided tumescence and manual tumescence in patients who underwent split thickness skin grafting.

Specific Aim # 3:

To quantify and compare perioperative transfusion requirements, and total blood loss formulaically, between machine aided tumescence with MD1 and manual tumescence, with MD2 in patients who underwent split thickness skin grafting.

Background

Tumescence provides a safe and easy to administer protocol to achieve various goals during skin grafting. Traditionally, it was established and widely used in the field of cosmetic surgery, specifically in liposuction. [20] Ease of use and positive outcomes have led to its adoption in multiple other disciplines. In September of 2016, the department of trauma surgery at Banner University Medical center (BUMC-T) began to utilize a novel technique in collaboration with perfusion services to aid in split thickness skin grafting procedures (STSG).

Consistent with population statistics, burn wounds accounted for the majority of our patient group. US population statistics for burn injuries are represented by 6 major categories respectively in decreasing prevalence: fire/flame, scald, contact, electrical, chemical, and other.[6] "Other" is mainly represented by radiation burns. Of the patients that require hospitalization for burn injuries, US population statistics for mortality was approximately 5%.[1]

Despite the relatively high mortality rate, overall mortality rates have been on the decline over the past two decades. Studies have shown that a large proportion of this reduction, can be attributed to education and the prevalence of smoke detection devices. Smoke devices alone, have been shown to reduce burn mortality by 75% and 60% for residential home fires. In addition, fire prevention programs and drills learned in school, such as "stop, drop, and roll" has helped lower overall incidence. However, given the intense course of medical management, prevention still remains the best strategy. [1]

As briefly mentioned earlier, patients that require skin grafting procedures from burns are often referred to specialized units due to the extreme complexity in medical

management. These type of injuries elicit profound changes in the physiological and metabolic state of all major organ systems. Multi-organ failure is the leading classification for mortality in the burn setting, and accounts for greater than 85% of deaths.[2] Burn wounds are dynamic and require multiple assessments. Various factors that can change the course of management include both intrinsic factors and extrinsic factors. Some of the more common intrinsic factors include the release of inflammatory mediators and bacterial infections. Extrinsic factors can include dehydration, hypotension, and thermoregulation as a result from a hyper-metabolic state or multi-organ dysfunction.[3] As such, it is critical to initially assess the depth of injury to plan out an optimal treatment plan. Wound depth is generally classified into one of four categories. These categories are: epidermal burns, superficial partial thickness burns, deep partial thickness, and full thickness injuries.

Epidermal Burns

Also known as a first degree burn, these type of burn injuries are typified by burns only on the epidermis. They are generally the mildest type of burn injury and when treated appropriately, can be healed rapidly, usually in less than a week by undamaged keratinocytes. Treatment usually consists only of mild analgesia.[3]

Superficial partial thickness burns

Injuries of this type is consistent with the upper dermis and epidermis. They are also known as second degree burns. Exposed nerves causes pain in this type of depth wounds, but healing usually occurs within two weeks. Thin hairless skin, such as on the eyelids typically heal sooner than thicker skin, such as those on the scalp. Superficial partial thickness wounds are characterized with blisters, moderate edema, moist surfaces

below blisters, and bright red colorization. Treatment generally consists of antimicrobial agents, and promotion of epithelialization with wound dressings to promote a moist environment.[3]

Deep partial thickness burns

Third degree burns cause wounds that are most difficult to treat and assess. They involve injury to the papillary and reticular dermis. They are characterized by broken blisters, excessive edema, moist surface, and red/white waxy colorization.[4] These wounds are treated in a similar fashion as superficial partial thickness burns, however excision and grafting is recommended.

Full thickness burn injury

Inconsistent to chronologic numerical convention, these injuries are still considered third degree, unless the injury extend to the muscle or bone. Similar to epidermal burn injuries, this category is straight forward, and easy to assess. In this type of injury, damage extends into the hypodermis and all regenerative elements are destroyed. Characteristics include charred, insensate, and eschar formation. Treatment almost always requires excision and grafting with a full thickness skin graft (FTSG), which includes the full thickness of the dermis. [4]

Skin grafts

Skin grafts have an extensive history, dating back over three thousand years ago. In India, it was common-place to punish thieves and adulterers with nose amputation. From the abundance of amputation injuries, historic surgeons would take grafts from the buttocks to reconstruct the injured area. These humble origins led to the first successful FTSG in 1804 when Gambacurta Boronio in Milan performed an autograft on a sheep.

Then in 1822, Bunger of Marlburg, successfully reconstructed a nose with a human autograft. In 1886, full thickness skin grafts were used to cover large wounds by Karl Thiersch in Munich. However, the first usage of a split thickness skin graft for burns was seen much later in 1942, when Brown and McDowell reported success in Philadelphia. Then finally, in 1964 Tanner, Vandeput, and Olley from Atlanta invented the technology to expand skin grafts, to effectively increase its surface area by up to 12 times through meshing.[5]

There are two general categories for skin graft procedures done at BUMC-T. Split thickness skin grafts, are grafts that include the epidermis and part of the dermis, with the dermal portion being variable. Full thickness skin grafts consists of the epidermis, and the entire thickness of the dermis.[6] Generally, STSG are taken as an autograft, which is a graft taken from one part of an individual's body and transferred to a different part on that same individual's body. Although these make up the majority of skin grafts, various other types can be used. Isografts are a type of graft taken from donors that are genetically similar to the recipient. Allografts are taken from donors of the same species as the recipient, while xenografts are taken from species different than the recipient.[5]

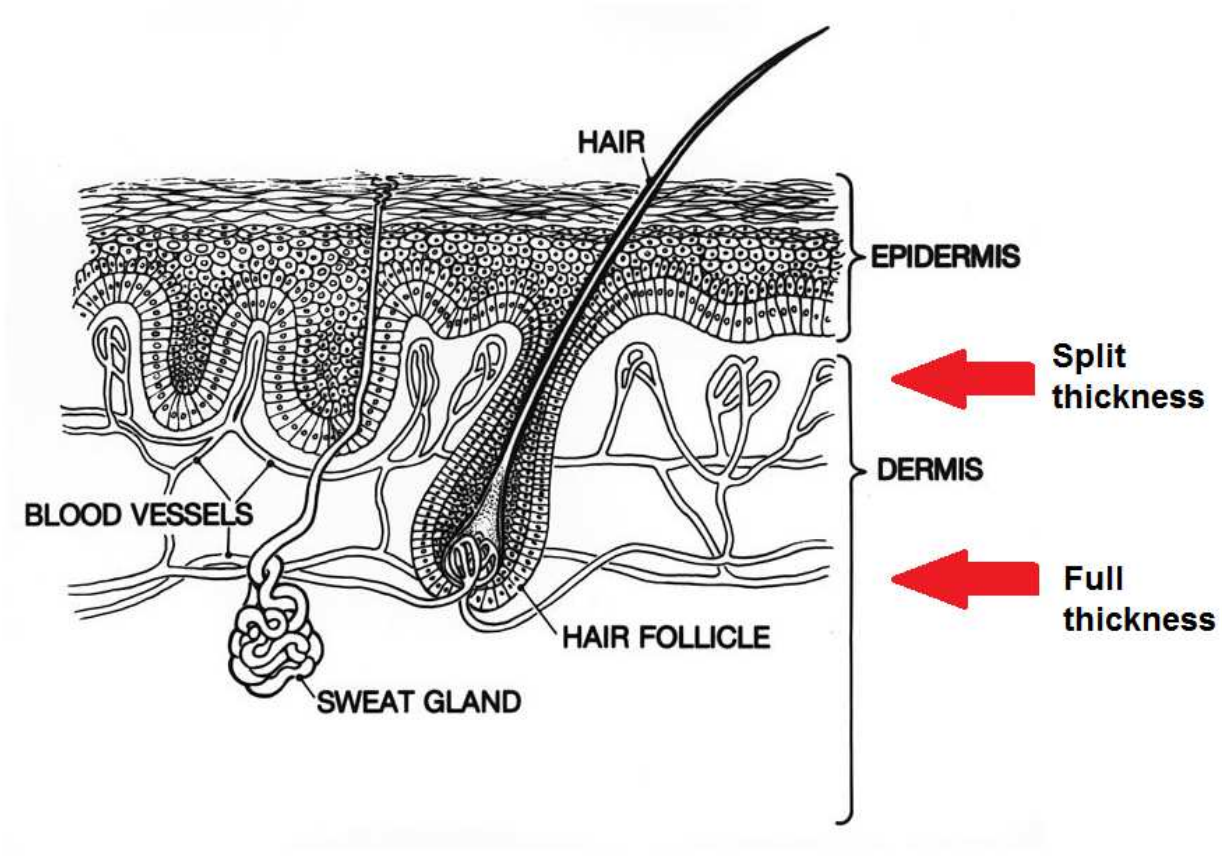


Figure 2 Skin cross section: Diagram of a cross-section of the skin, demonstrating split thickness and full thickness skin grafts. National Cancer Institute. B&W, Medical Illustration.

Graft take

The end goal for skin grafting is similar for all types of grafts. The success of which is collectively determined by the graft take, which is defined as the survival of a graft based off of plasmatic imbibition, inosculation, primary and secondary revascularization. In plasmatic imbibition, a STSG is nourished by plasma exudate from the donor site during the first 48 hours of grafting. During this phase, STSGs are able to withstand an initial ischemia time longer and better than an FTSG.

During inosculation, at around 48 hours, a vascular network is established in the fibrin layer between graft and recipient bed. Capillary beds from recipient site and graft make contact and form open channels. Blood flow is established and the graft turns pink. Failed anastomoses results in continued proliferation of capillaries. During this phase, necrotic material, excessively thick fibrin layers, hematoma, seroma, or air at wound bed may prevent anastomoses.[5]

Primary revascularization is best characterized by afferent and efferent differentiation, which generally occurs 4-7 days post grafting. Secondary revascularization occurs when anastomoses between donor and recipient bed is delayed or prevented. Indications of secondary revascularization include: granulation tissue, smooth, fibrotic, tight, and a slick silvery sheen representing cicatrix (scar) within the graft. In a randomized trial from the University of Nairobi, 80 patients undergoing STSG were split into a tumescent and non-tumescent technique using epinephrine and saline solutions. When evaluated up to three weeks post-grafting, it was shown to be a statistically significant ($p=0.011$) increase. Graft take was increased by 2.3% from 94% to 96.3% in the tumescence group. [7] Initially, a similar enterprise was initiated at BUMC-T,

but was ultimately omitted due to lack of adverse graft take events. From September of 2016 through March of 2018, graft take was 100% for all patients who underwent STSG procedures at BUMC-T.

Tumescent technique

There are multiple ways to achieve tumescence, the most common ways include roller pump, hand pressure, and pressurized IV. Regardless of the specific method, the end goal of tumescence is to aid in hemostasis, maintain local anesthesia, and facilitate dermatome or blade mediated auto-graft harvest. All methods involve the subcutaneous infusion of a solution. Of notable benefit for the roller pump group was ease of delivery and shorter infusion durations. Manual tumescence, either by hand pressure or pressurized IV systems require an additional level of operation. In the former, multiple refills are required and in the latter, IV change-out followed by re-pressurization was required.

After sufficient tumescence was achieved, mineral oil was applied topically to the donor site and electric dermatome mediated autograft harvest was initiated. A dermatome is one of a few essential grafting devices for surgeons. The principle of the device is to provide a variable thickness graft calibrated to the thousandths of a centimeter. It utilizes a rotating blade in order to provide a suitable graft. Alternatively, a knife may be used, but has largely fallen out of favor with surgeons in North America. [25]

Pharmacology

Epinephrine, which is a sympathomimetic catecholamine is a widely used agent in the clinical setting. It is also the main active constituent used in the majority of tumescence solutions. Epinephrine is formed in the adrenal medulla of humans, and stimulates both

alpha and beta adrenergic receptors to cause systemic vasoconstriction. Additionally, it can cause gastrointestinal relaxation, stimulate the heart, and dilate bronchi/cerebral vessels. In the skin graft clinical setting, epinephrine is used both as a vasoconstrictor to induce hemostasis, and to maintain localized anesthesia.[8] Many formulations exists, generally ranging 1-2 mg of epinephrine diluted 1:1,000,000 or 1:500,000 in normal saline or lactated ringers solution. The latter, is termed Pitkin's solution.[23] Patients have been reported to tolerate these dosages of epinephrine well, however care must be taken to account for anesthetic agents used as they can increase the risk of arrhythmias. Studies have indicated 50% of patients will experience arrhythmias at epinephrine dosages of 2, 4, and 7 micrograms/kg with halothane, enflurane, and isoflurane, respectively.[9]

Phenylephrine is a sympathomimetic amine that acts as an alpha adrenergic agonist. It is widely used as a nasal decongestant, and can aid in the clinical setting by acting to temporarily relieve hypotension. It is not widely used as an agent for tumescence due to the much more practical and profound effects of epinephrine with little to no adverse effects with therapeutic dosages. However, studies have indicated that phenylephrine can be used effectively to induce hemostasis and maintain local anesthesia. Mitchell et al. was able to demonstrate with a dose response study that the optimal dosage to induce hemostasis for STSG with phenylephrine is 5 micrograms per milliliter.[10] However, the availability of a superior agent for hemostasis, has prevented widespread research for phenylephrine as an alternative agent for skin grafting. Only 6 observations were documented and of those limited sample sizes, only small burn areas that were less than 5% total burn surface area was included. Additional studies with larger

sample sizes will need to be completed before phenylephrine can be universally accepted as an alternative to epinephrine in this setting. [10]

Figure 3 Pitkin's solution: Pitkin's solution consists of Lactated Ringers and 1 mg epinephrine for a dilution of 1:1,000,000. Typical volumes of infusate at BUMC-T is 0.7 L, however this is highly variable.[23]

Methods

Operative management

Following induction of anesthesia, the patient was sterilely draped. Shortly after, tangential excision and debridement was started at the recipient site to remove necrotic fat and skin. During this point hemostasis was achieved by either tourniquet or topical epinephrine with thrombin spray, depending on the site of injury. Upon adequate debridement, the donor site was prepared for hemostasis with MAT. At the start of tumescent infusion, the roller pump was set to deliver 150 mL/min of tumescent solution through ¼" tubing attached to an 18 gauge spinal needle until the tissue was properly tumescent as determined by the surgeon. At this point dermatome mediated auto-graft harvest was started. Donor site was treated with antibiotics and xeroform, a type of non-adhesive gauze. For MT groups, all procedures except tumescence creation was the same. In the MT group, tumescence was achieved manually with saline at the donor site.

A Terumo Sarns 8000 roller pump utilizing a modified LivaNova CSC 14 4:1 cardioplegia circuit with stainless steel 2500 mL/min rated flow heat exchanger was used. The blood phase was clamped out to allow for full crystalloid delivery and effectively transformed the circuit into a single 1/4" inflow tube with a positive displacement between 150-200 mL/ min.

Figure 4 MAT devices: (Top) Terumo Sarns 8000 roller pump. (Bottom Left) LivaNova CSC 14 4:1 cardioplegia circuit with stainless steel 2500 mL/min rated flow heat exchanger. (Bottom Right) Micro-Temp LT Cincinnati Sub-Zero heat therapy heater system.

A Micro-Temp LT Cincinnati Sub-Zero heat therapy heater system was connected to the cardioplegia unit's heat exchanger port with 2L sterile water and was set to 42 C. The temperature was mildly hyperthermic as patients undergoing split thickness skin grafting are deficient in auto-thermal regulation. 1.0 mg epinephrine was added to 1.0 L Lactated Ringers solution to induce vasoconstriction and reduce blood loss. Total volume was highly variable, with high ranges of 6 liters.

Retrospective review of CBL and intra-operative temperature

After obtaining Institutional Review Board (IRB) approval, a retrospective chart review was conducted for patients who underwent STSG procedures at BUMC-T from September 2016 – March 2017. Patients were included from two groups: those that underwent MAT with surgeon 1 (MD1), and those who underwent MT with surgeon 2 (MD2), both of whom, were at the time BUMC-T trauma surgeons from the division of Trauma surgery. Patient data bank information were provided by MD1, and data abstraction was done via CERNER and EPIC EMR, which were provided by BUMC. The parameters on figure 5 were abstracted, and stored de-identified onto University of Arizona BOX, and maintained physically on institutional computers. The expanded definitions for patient population, procedures, and justification of calculations are available in the summary figure located in appendix A, B.

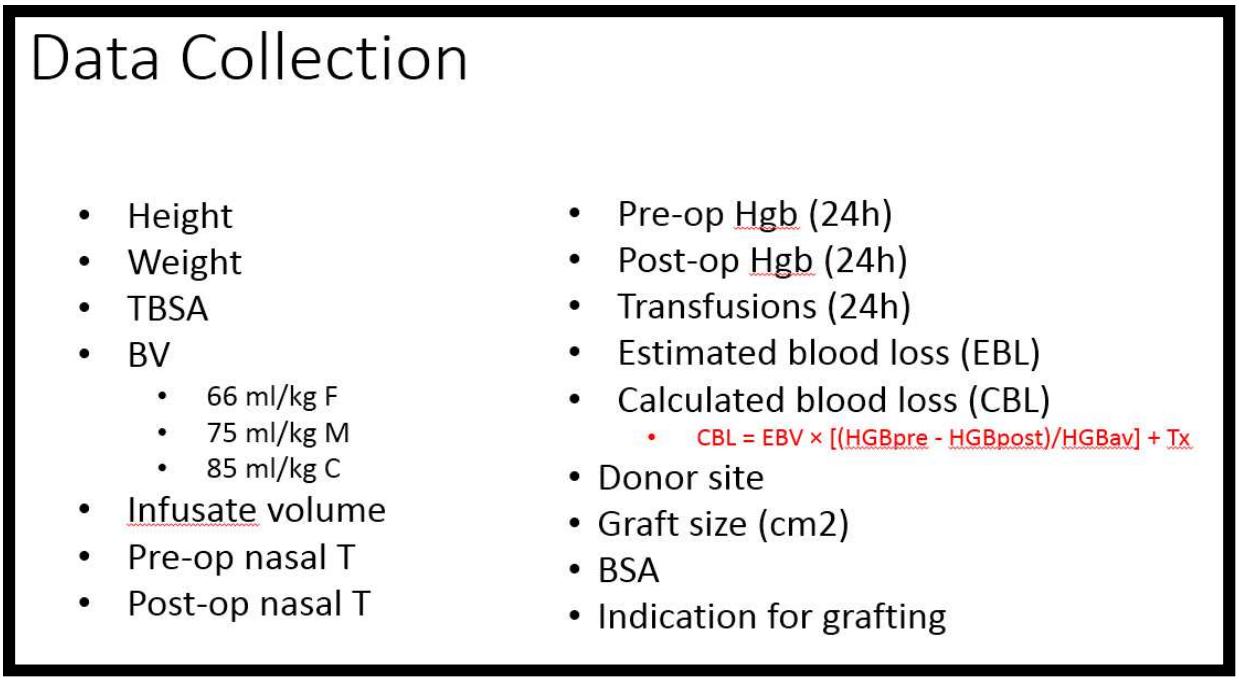


Figure 5 Data Collection: Summary of collected variables with added definitions for blood volume and CBL.

The MAT group included 43 observations, while the MT group had 19 observations. Exclusion criteria included: missing graft types, unmatched graft sizes, unmatched donor site, coagulopathy, and declination of blood products, xenografts, allografts, FTSG, and patients who underwent more than one surgery in a 48 hour period.

Intraoperative temperature was pulled from anesthesia records. Time points were obtained immediately pre-operatively in the OR, and at the end of surgery in degrees Celsius. From this data, intra-operative temperature changes were determined. For detailed summary of data, see appendix C.

Transfusion records were obtained intra-operatively from anesthesia records, while post-operative amounts were obtained from either physician progress notes, or RN progress notes intake/output forms. Perioperative transfusions were given as either whole

blood or packed red blood cells. They were documented either in units or mL. In order to standardize these amounts, whole blood was estimated as 40% hematocrit, while packed red blood cells were 60%. A unit was defined as 350mL, which was the typical volume at BUMC-T. From these assumptions, a simple conversion was conducted to express calculated blood loss (CBL) in mL of whole blood. CBL values were then all standardized to per unit square centimeter of graft. CBL formulations was originally described and validated by Bundy et. al, in 1993.[11] Since then it has been validated by numerous other sources and represent the current gold standard of calculating blood loss during burn surgery. However, the original formulation by Bundy utilized pre-operative hemoglobin in the denominator instead of an average as shown below. Recently, Cartotto et al. modified the formula to account for increased operative times and current medical management of patients.[12] The original formula implies that the decrease in hemoglobin was equivalent to the fraction of the total blood volume lost, and that the formula only applies if all shed blood has the same initial Hgb concentration. Increased intraoperative times often requires fluid resuscitation and large volumes on tumescent infusate, hence, the shed blood was increasingly diluted. The modified formula below attempts to account for this.

$$CBL = BV * [(Hgb_0 - Hgb_1)/Hgb_{av}] + tx$$

Figure 6 Modified calculated blood loss formula: Modified calculated blood loss formula validated and described by Cartotto et al to include to increased hemodilution.

BV was blood volume, Hgb_0 was pre-operative hemoglobin, Hgb_1 was 24 hour post-operative hemoglobin, and Hgb_{av} was the average Hgb between the former. Tx was total transfusions within 24 hour post-operative.

STSG size information was pulled from surgical reports of the respective surgeon and expressed in squared centimeters. Data was either provided in exact amounts or given as a proportion of BSA. In those instances, BSA was calculated as:

$$BSA\ (m^2) = \sqrt{\frac{Ht\ (Cm) \times Wt\ (kg)}{3600}}$$

Figure 7: Body surface area formula

Infusion pressure characterization

In order to characterize intradermal perfusion pressures in-vivo with MAT/MD1, we constructed an additional modification to our roller pump setup. By attaching a pressure transducer to the superior portion of the CSC heat exchanger unit, we recorded data every second during subcutaneous infusion. Units were expressed in mmHg and then graphed as pressure over time.

We did not measure in-vivo pressures for MT/MD2, however, we simulated MT in-vitro over the course of 60 seconds by attaching a pressure transducer to three-way stopcock and 60 mL syringe with 18G spinal needle. Infusate used for both in-vitro and in-vivo determination was the same formulation, i.e. clinical Pitkin's solution.

Prospective in-vitro determination of infusion duration

A total sample size of n=30 was used with 15 standard manual infusion and 15 roller pump infusion. Three operators were each randomly assigned 5 standard infusion

trials, and 5 machine infusion trials. A timekeeper was used to determine the duration of each trial. To account for bias and conflict of interest, a double blind study design for either MAT or MT was used for all participants at the start of every subsequent infusion.

At the start of tumescent infusion, the roller pump was set to deliver 150 mL/min of tumescent solution through ¼ tubing and an 18 gauge spinal needle. Machine infusion was delivered indefinitely until 0.7 L of tumescent solution was exhausted.

At the start of standard manual infusion, tumescent solution was delivered with a 60mL syringe through an 18 gauge needle. The operator also refilled the syringe until 0.7 L of tumescent solution was exhausted.

Analysis

For all parameters, mean +/- standard deviation were calculated. A p-value was used to indicate the statistical significance of a result. Using STATA, a two sample t test with unequal variances was used for continuous data. Statistical significance was determined if the p value was less than 0.05. Calculated blood loss was determined formulaically, after the exclusion criteria was fulfilled. Additionally, for CBL and transfusion results, data was determined before and after utilizing a sub-group analysis. Using histograms created with Microsoft excel, STSG size and donor site were compared between the MAT and MT group. Unmatched graft sizes and donor sites were removed.

A linear regression model was then generated for these independent variables age, weight, BSA, percent BSA grafted, graft size and dependent variable CBL separately for MAT and MT. The dependent variable (CBL) was on the Y axis whereas

the independent variable was on the X axis. Results were presented on a scatterplot with standard best fit line. A p value less than 0.05 was considered significant and represented a meaningful correlation between dependent and independent variable. Linear regression analysis with significant results were than analyzed by two sample t test with either unequal or equal variance in order to determine if variables were well matched.

Results

Intraoperative temperature

For the intraoperative temperature analysis, there were 62 total observations with n = 43 in the MAT group and n = 19 in the MT group. Starting patient bladder temperatures were similar in both groups with a mean of 36.76 +/- 0.78 C for the MAT and 36.92 +/- 0.99 C in the MT group. Mean post-operative bladder temperatures were significant lower in the MT group, which was 35.55 +/- 1.16 C compared to 36.58 +/- 0.78 C. A mean of 35.55 C in the MT group, represents both statistical and clinical significant due to the proximity to defined clinical hypothermia at 35 C ($p \leq 0.0001$). Mean temperature changes for the MAT group was -0.181 +/- 0.70 C compared to -1.35 +/- 0.85 C for the MT group. For full data summary, see appendix C, Table 3.

Infusion duration

For the in-vitro infusion duration analysis, there was a total of 30 observations. For MT, n = 15. The mean time required to infuse 700 mL of tumescent solution through an 18 g spinal needle and 60 mL syringe manually was 1156 +/- 64 seconds, with the shortest time at 1068 seconds and longest time at 1281 seconds. In the MAT, n = 15, with a mean of 278 +/- 1 second, which represents a 74% decrease in duration. ($p \leq 0.0001$)

Calculated blood loss

Initial calculated blood loss had a total n = 50, with 31 in MAT and 19 in the MT group after exclusion of data with missing lab values. MAT group had a mean CBL of 1.17

± 1.19 mL/cm2 compared to 0.45 ± 0.47 mL/cm2. (p = 0.02) Refer to Appendix C for complete data summary.

From here, a subgroup analysis was completed for graft size and donor site. Results revealed that MAT and MT were not well matched for either. MAT was shown to be completely unmatched after 1600 cm2 grafts.

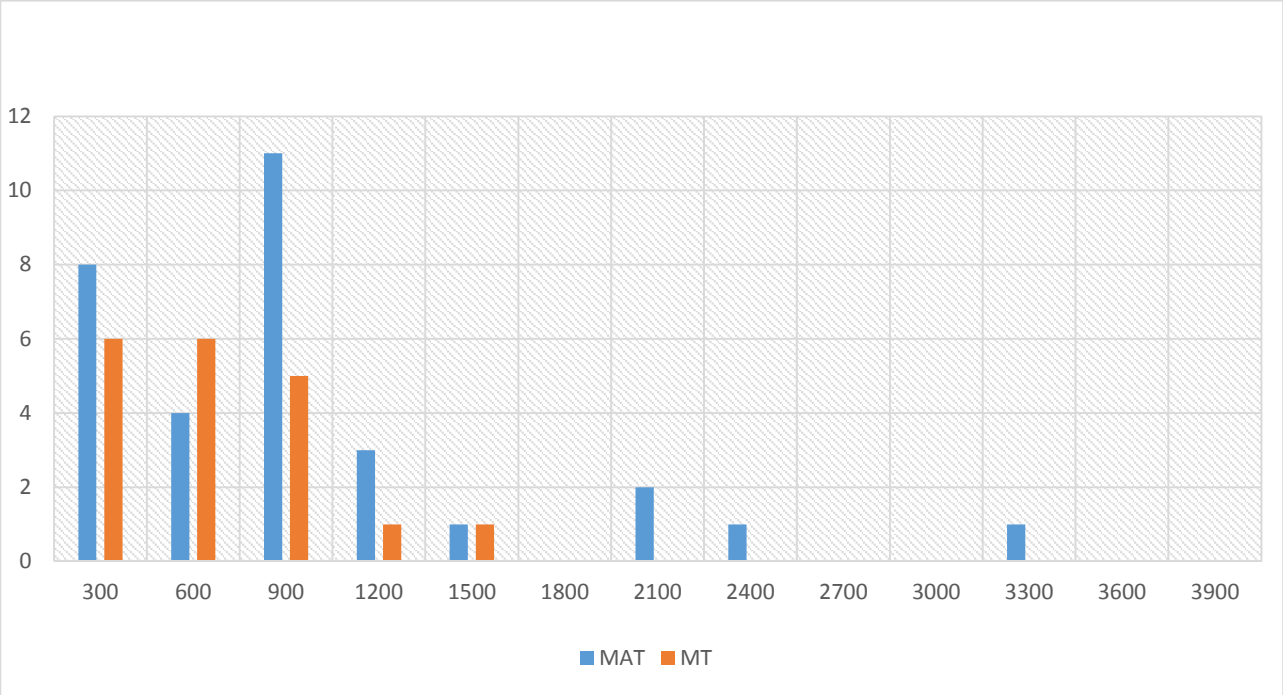


Figure 8a Graft size histogram: Stratifies procedures done with MAT and MT into graft sizes of 300 cm^2 intervals. MAT was clearly shown to be used for larger graft sizes compared to MT in at least 4 procedures.

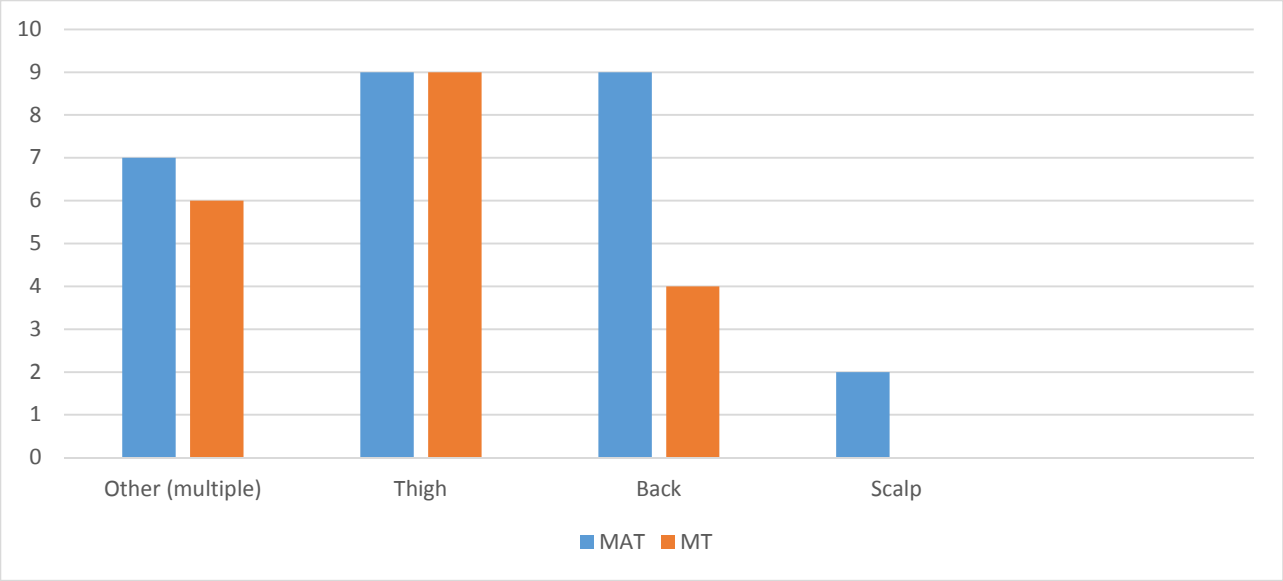


Figure 8b Donor site histogram: Stratifies procedures done with MAT and MT into donor sites due to potentially increased bleeding in certain sites. Scalp procedures are well known within the surgical community to be higher for blood loss. "Other" columns represent procedures where multiple sites were used and standardization not possible.

Donor sites were separated by four groups, with "other" representing operations where multiple donor sites were utilized and standardization was not possible. The categorization of other, thigh, back, and scalp revealed that the scalp as a donor was unmatched. After accounting for outliers for both graft size and donor site, total n = 33 with n = 20 in the MAT and n = 13 in the MT group. Further analysis revealed that results were largely unchanged with mean 1.1 ± 0.98 mL/cm2 for MAT and 0.55 ± 0.54 mL/cm2 for MT. (p=0.08) For summary of calculation after exclusion of unmatched graft size and donor sites, see Appendix C Table 5.

Intra-operative Transfusions

Transfusion requirements were significantly higher in MAT group 24 hour post-operative with mean 276 ± 316 mL pRBC compared to 43.5 ± 94.3 mL pRBC in the MT group. For MAT n = 18 and MT n = 13. A p value of *0.016* was obtained. A conversion to

whole blood was calculated to represent shed blood, and resulted in a mean of 414 ± 474 mL in the MAT group and 65 ± 141 mL in the MT group.

Linear regression models ran for 12 variables against CBL resulted in no significant values at p less than 0.05. However, MD1 percent BSA grafted was the only variable that came remotely close to significance at p = 0.058. Two sample t test with unequal variance for MD1 percent BSA grafted vs MD2 percent BSA grafted then resulted in a p value of 0.19. For linear regression and correlation analysis see Appendix C, Table 6.

Infusion pressure determination

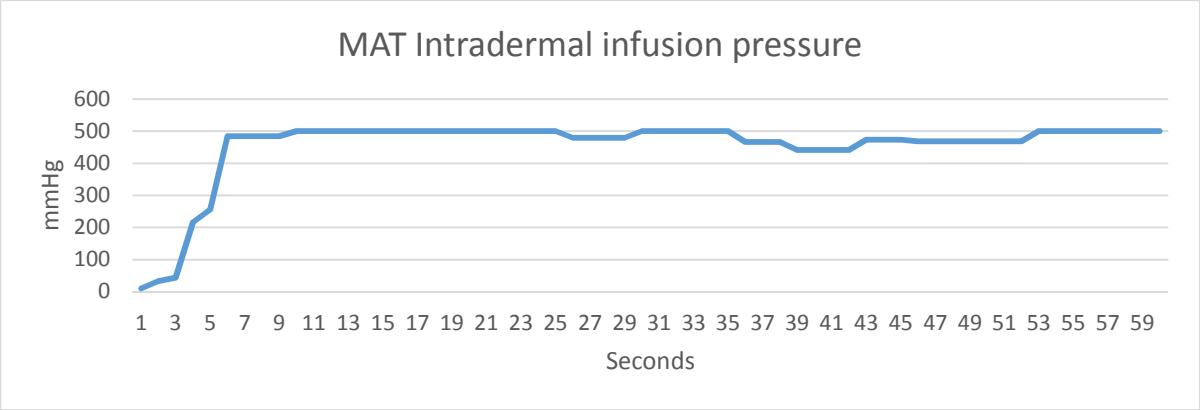


Figure 9a: MAT Intradermal infusion pressure

Over a duration of 60 seconds MAT generation, intradermal pressure readings were elevated past 500 mmHg at 150mL/min of flow. Due to transducer specifications, pressure readings were limited to a maximum of 500 mmHg.

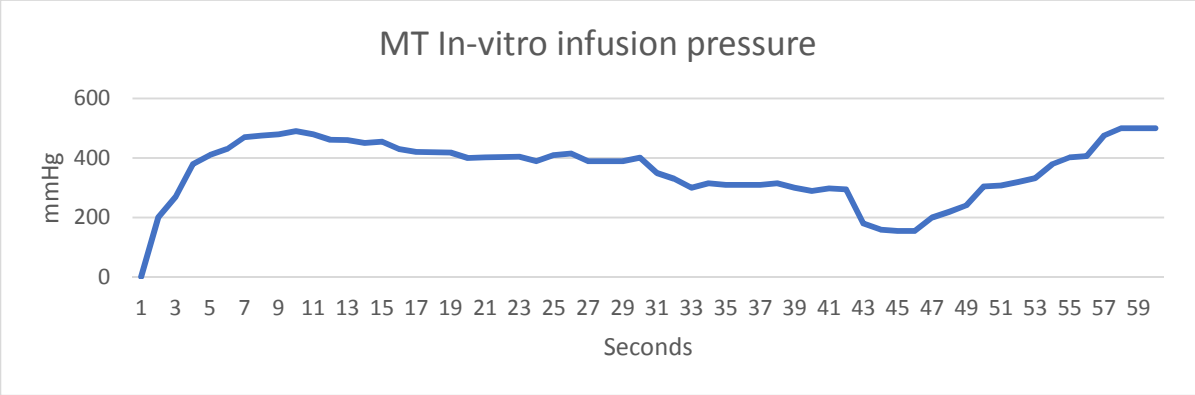


Figure 9b: MT in-vitro infusion pressure

Over a duration of 60 seconds MT generation, in-vitro pressure readings were variable and generally less than 500 mmHg. Due to transducer specifications, pressure readings were limited to a maximum of 500 mmHg.

Summary

MAT

Calculated Blood loss

1.1 ± 0.98 mL/cm2

24 hour post-op transfusions

276 ± 316 mL pRBC

Infusion duration (0.7L)

1156 seconds

Intraoperative T regulation

Preop: 36.7 C°

Postop: 36.6 C°

Intraoperative change: -0.18 C°

MT

Calculated blood loss

0.55 ± 0.54 mL/cm2

24 hour post-op transfusions

43.5 ± 94.3 mL pRBC

Infusion duration (0.7L)

280 seconds

Intraoperative T regulation

Pre-op: 36.9 C°

Postop: 35.6 C°

Intraoperative change: -1.36 C°

Specific Aim #1:

To quantify and compare infusion time required to create tumescence between machine and manual infusion, in patients who underwent split thickness skin grafting.

Machine aided tumescence (MAT) reduced infusion duration significantly, compared to manual tumescence (MT) from 1156 seconds to 280 seconds for 0.7 L of infusate.

<u>Specific Aim #2:</u> To quantify and compare intraoperative temperature changes between machine and manual infusion, in patients who underwent split thickness skin grafting.

Machine aided tumescence was superior to manual tumescence for intra-operative temperature regulation and showed a significantly lower intraoperative temperature change. Despite having similar pre-operative bladder temperatures maintained by the same anesthetic team, post-operative temperatures in the MAT was 36.6, which represented a -0.18 degree C change from pre-operative temperatures. Comparatively, MT group post-operative temperature was 35.6 degrees and represented a

-1.36 degrees C change.

<u>Specific Aim # 3:</u>

To quantify and characterize perioperative transfusion requirements, and total blood loss formulaically, between machine and manual infusion, in patients who underwent split thickness skin grafting.

No comparisons can be made due to confounding factors regarding the test group and control. Unlike previous comparisons, surgical management was not completed by the same team or individual. However, in this specific instance MD1 for the MAT group demonstrated significantly higher CBL and transfusion requirements than MD2 for the MT group at 1.1 ± 0.98 mL/cm2 and 276 ± 316 mL pRBC transfusion requirement, whereas MD2 with MT demonstrated 0.55 ± 0.54 mL/cm2 CBL and 43.5 ± 94.3 mL pRBC transfusion requirement.

.

Discussion

General widespread effects of perioperative hypothermia include immune depression (which can increase likelihood of wound infection), decreased perfusion (which can decrease graft take), prolonged hospitalization (increased costs and time), and decreased platelet function (resulting in coagulopathy).[14]

Clinical hypothermia is determined when core body temperature drops below 35 degrees C. In scenarios for medical management, hypothermia is actively sought out. For example, during an emergent aortic dissection, cerebral injury, or neonatal encephalopathy. [13] In those specific instances, hypothermia can be required for intervention. However, in the burn and traumatic complications involving large areas of the body, hypothermia was meticulously avoided and heavily scrutinized perioperatively. Increased morbidity and mortality from unwarranted clinical hypothermia is alone worth further study.

To this end, our goal was to quantify intraoperative temperature fluctuations, and tumescence infusion duration with a modified technique designed to increase outcomes based on both fronts. Gradually, we expanded the project to include graft take data and blood loss information. Fortunately, graft take as defined by various hallmarks such as vascularization and angiogenesis was nearly 100% during the duration of this study at BUMC-T.

Blood loss has long been determined to be a major complication of skin graft surgery. Many studies have been completed in an attempt to quantify and describe the loss. Sterling et al concluded that from 229 possible reviews of blood loss during just

burn surgery, that 27 are dedicated to methods of hemostasis. [17] However, even in such an extensive review, none of them described a technique similar to the roller pump aided method.

To compound the importance of adequate hemostasis during STSG, are the risk factors of allogeneic transfusions. Although the risk of blood transfusion complications have been severely reduced over the last few decades, zero risk transfusion was not achievable. In fact, at least three types of hepatitis viruses are transmissible by all blood components. A brief list of complications can include the following in decreasing order of prevalence: minor allergic reactions, bacterial infections, viral hepatitis, hemolytic transfusion reaction, HIV infection, acute lung injury, anaphylactic shock, fatal hemolytic reaction, graft vs host disease, and immunosuppression. [18] The last, but very feasible concern was monetary and logistical costs of blood products.

During our review of data, we found that intraoperative temperature management for STSG was completed by the same team of anesthesiologist working under similar protocols. Temperature was measured at the bladder, and actively kept above 35 degrees C. OR ambient temperatures were generally kept at 27 degrees C. Most importantly, we determined that pre-operative core temperature was similar in both MAT and MT groups. We were able to conclude that post-operative temperatures in the MAT was 36.6, which represented a mean -0.18 degree C change from pre-operative temperatures. Comparatively, MT group post-operative temperature was 35.6 degrees and represented a mean -1.36 degrees C change. This was clinically significant because hypothermia was defined by either 35 or 36 degrees core temperature depending on the institution. In this instance, heating strategies were largely similar with

one notable difference. The tumescent solution used and infused was generally larger and always warmed to at least 37 degrees C, whereas MT utilized room temperature infusate. The ambient infusate was measured to be approximately 22 degrees Celsius in one instance. Additionally, an active recirculation technique was used in the MAT group, which involved continuously running the solution through the CSC heat exchange unit set at 42 degrees C. With such definitive results, further studies should focus on validating and drawing a correlation with the tumescent solution. It is our recommendation that records of infused volume should be analyzed to further conclude that superior temperature management was achieved by virtue of our modified heater unit alone.

Multiple studies have indicated an inversely proportional relationship between operative duration and patient core temperature.[14-16] This makes reducing operative duration a viable option for temperature management. Manual tumescence requires an

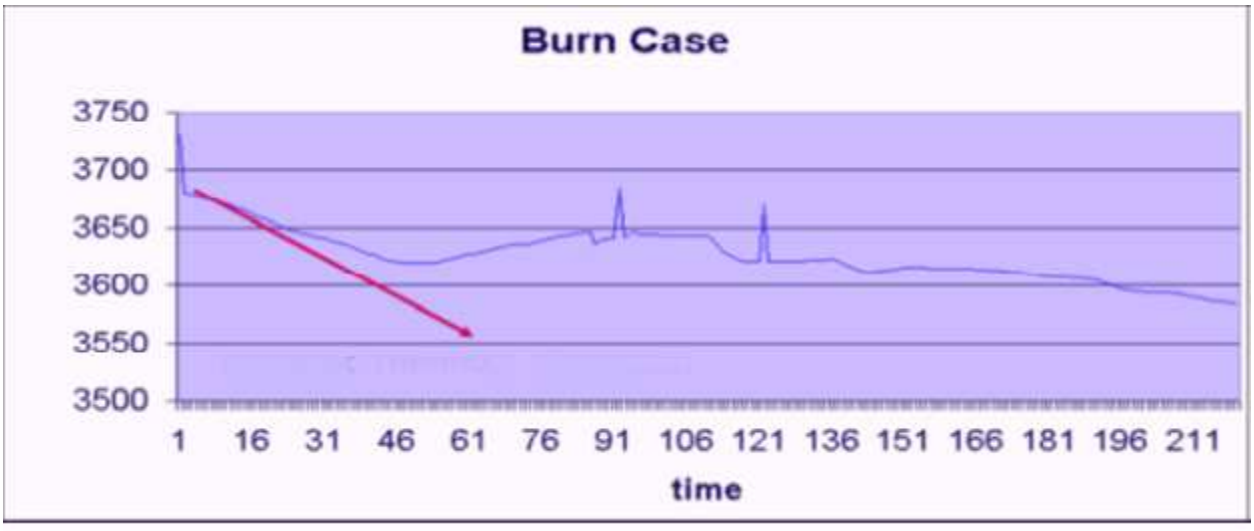


Figure 12: General Burn case temperature change over time.[16]

excessive effort in addition to additional time required for infusion because the operator has to continually refill the syringe. To quantify this infusion time, we recorded the time required to infuse 0.7 L of tumescent solution, which was the average amount infused as determined by MD1. However, it was not uncommon to encounter larger grafting areas that required significantly more infusion volume. In fact, during our clinical activities, we have utilized up to 6L of infusate per procedure. With average measurements of 1156 seconds, that would be nearly 9900 seconds or 165 minutes of infusion not accounting for fatigue! Obviously, this was not feasible. Even at 1156 seconds or about 19 minutes, this represent a large portion of the procedure. MAT eliminates the fatigue factor, and the requirement to refill the syringe. At an average infusion rate of 150 mL/min, it accomplishes the same volume infusion in 280 seconds, which was a 76% decrease in infusion duration. Least of all, was cost savings which by itself was not insignificant. Multiple studies in this area have identified figures between $62 and $500 per minute of surgery. [19]

Calculated blood loss and transfusion requirements was not as straight forward as our two other values. An extensive literature review showed overwhelming support for tumescence hemostasis. Even though none of them studied roller pump, we simply assumed that more efficient tumescence generation with roller pump would follow literature results for other methods of tumescence generation. The results were surprising for CBL and transfusion requirements in the MAT/MD1 group, which was un-expectantly high. Due to such events, multiple linear regression analyses were completed for variables that were suspected of skewing the data if unmatched. Age, weight, BSA, pre-operative hgb, graft size, and percent BSA grafted were reported with scatter plot and

best fit line separately for MAT and MT. Of the 12 variables analyzed, only percent BSA grafted for MD1 came close to significance at 0.058 and a negative slope. This suggests that there was a possible inverse correlation for percent BSA grafted and CBL/cm^2. However, this would only be relevant if the sample population for MT was unmatched. To determine this, two sample t test with equal variance was completed for MD1 percent BSA grafted and MD2 percent BSA grafted. The result was a p value of 0.20 meaning the patient sample population was matched. In other words, we were able to mathematically prove that the variables used would not have significantly affected the data, even if it was unmatched. Even after scrutinizing the data and analyzing subgroups, the results were the same. In order to provide perspective to the surprising results for CBL and transfusions, we attempted to characterize intradermal infusion pressure. By attaching a pressure transducer onto our circuit, we were able to describe the intradermal pressure readings over the course of a 60 second infusion at 150 mL/min.

Although, pressure readings were limited to a maximum of 500 mmHg, our results indicated that MAT pressure readings were consistently elevated above MT. CBL and transfusions requirements were significantly higher for MD1 and MAT than expected. This may be due to the elevated and sustained intradermal infusion pressure that could potentially cause excessive microvascular damage and thus, diffuse micro-hemorrhaging. The work completed on this topic offers a perspective to the issues of bleeding, and indicates the need for more careful study. Ideally, a randomized prospective comparison where each patient serves as their own control for MAT vs MT should be completed. The surgeon would be need to be the same, and have an active role, along with the perfusionist and anesthesiologist, to estimate average blood loss in addition to

formulaic estimation. Patient populations and parameters should be well matched, and data for excision/debridement need to be accounted for. Finally, lab values for hemoglobin need to be measured at the same time points, which is immediately before surgery, and exactly 24 hour post-operatively.

In conclusion, our work has raised concerns that indicate more rigorous studies with regards to blood loss and transfusions need to be completed before machine aided tumescence can be recommended for widespread use. For the patient population that may benefit from better temperature management, such as pediatric patients with a large TBSA, we have determined that MAT is superior in due to enhanced temperature regulation and shortened infusion durations.

Appendix A: Sample population

MAT					
Variable	Obs	Mean	Std. Dev.	Min	Max
MD1age	9	37.11111	28.45524	4	75
MD1wt	9	62.91111	34.31284	14.1	95.5
MD1BSA	9	1.594227	0.6542372	0.6308196	2.15646
MD1prehgb	33	9.357576	1.435277	7.1	13.4
MD1graftsize	31	839.31	691.4626	94.62293	3200
MD1BSAgraft	31	0.0670682	0.0442576	0.0115931	0.1674957
MD1StartT	43	36.76744	0.7851967	34.4	38.2

Table 1a: MAT/MD1 patient parameters

MT					
Variable	Obs	Mean	Std. Dev.	Min	Max
MD2age	5	30.2	19.07092	6	59
MD2wt	5	60.68	26.64652	21.4	91
MD2BSA	5	1.626455	0.4981818	0.8197561	2.070988
MD2prehgb	18	8.994445	1.293637	6.9	11
MD2graftsize	18	572.2222	307.8893	185	1348
MD2BSAgraft	18	0.0502908	0.0421842	0.0124045	0.1799735
MD2startT	18	36.91111	1.027212	33.9	38.4

Table 1b: MT/MD2 patient parameters

Appendix B: Data description

Description of data

Start intraop T : Units for T is in Celsius, and is pulled from intra-op anesthesia records

End Intra op T : Units for T is in Celsius, and is pulled from intra-op anesthesia records

Delta T start to finish: Mean T change in Celsius from end intra op T - start intra op T

24hr preop hgb: Lab values are pulled as close to surgery as possible and typically not surpassing 24hr pre-op. However 1-2 patients had limited lab values. These patients were included if their lab values are consistent and they only had one surgery/bleeding event in that lab period. If lab values were consistent and non-fluctuating, but surpassed 3 weeks - they were omitted regardless.

24hr post op hgb: Lab values are pulled as close to 24h post-op as possible. However 1-2 patients had limited lab values. These patients were included if their lab values are consistent and they only had one surgery/bleeding event in that lab period. If lab values were consistent and non-fluctuating, but surpassed 3 weeks - they were omitted regardless.

24hr post op transfusions: This value was obtained from intra-op anesthesia records, progress notes, and Intake/outtake records within 24 hour post op. Transfusions were given either in whole blood or prbc. To standardize units, a "unit" was considered 350 mL. WB was considered 40% Hct, and pRBC was considered 60% hct. As such a conversion of 3/2 was used to change prbc to whole blood expressed in mL. For example 1U pRBC = 350mL*3/2 = 525 ml whole blood. Transfusion data is expressed in whole blood.

CBL: Calculated blood loss is determined formulaically: Blood volume * ((Hgb0-Hgb1)/Hbgav) + transfusions. Hgbav is the average between Hgb0 and Hgb1. This accounts for increased hemodilution as surgery gets prolonged and increased fluid resuscitation is required. Blood volume was calculated as 75*kg for males, 66*kg for females, and 85*kg for children under 18 years old. Although the 18 year old may not be well matched for 85*kg. The only children in the study was 4,5,6 years old.

Donor site: Donor site was included per operative note when available. For final data calculations, unmatched donor sites were excluded. Un-match sites also includes procedures where many sites were used and a standardization for MAT and MT was no possible. For final data calculation, donor sites were integrated into either Back, Thigh, or Scalp for an attempt at matching. Ex. Upper leg got categorized as thigh. In final data summary, xenografts and allografts were excluded if they represented the entire procedure.

Excised area (cm2): Data here was not used for final calculation due to inconsistency of documentation. This data represents total area excised including tangential excision, debridement, and STSG. STSG was always documented but excision and debridement were not.

Surgical graft (cm2): This data represents only STSG taken and grafted expressed in cm2, and pulled from operative notes.

BSA m2: Patient body surface area in m2

BSA cm2: Patient body surface area in cm2

Excised area per BSA: Percent excised (excision, debridement, graft) to BSA. Data not used for reasons above.

GraftareaperBSA: Percent graft by BSA

TBL2ml/cm2graft: Calculated blood loss standardized to cm2 grafted

Appendix B. Table 2: Definitions of data collected

Appendix C: Data summary and calculations

```
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev. [99.9% Conf. Interval]
---------+--------------------------------------------------------------------
MD1temp~a |      43   -.1813954    .1069178    .7011067   -.5596433    .1968524
MD2temp~a |      19   -1.363158    .1960443    .8545372   -2.131974   -.5943415
---------+--------------------------------------------------------------------
combined |      62   -.5435484    .1174743    .9249938   -.9496916   -.1374052
---------+--------------------------------------------------------------------
    diff |            1.181762    .2067279                .4664425    1.897082
------------------------------------------------------------------------------
    diff = mean(MD1tempdelta) - mean(MD2tempdelta)                t =
5.7165
Ho: diff = 0                                     degrees of freedom =       60

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0001          Pr(T > t) = 0.0000
```

```
 Variable |        Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
    MD1startT |         43    36.76744    .7851967       34.4       38.2
      MD1endT |         43    36.58605    .7845477       34.6       38.5
    MD2startT |         19    36.92105    .9992103       33.9       38.4
      MD2endT |         19     35.5579    1.160611       32.6       37.3
```

Appendix C. Table 3: Intraoperative temperature change summary: Two sample t test with unequal variances, means, standard deviation, and 99.9% confidence intervals for summarizing pre-op, post-op, and intra-op temperature changes.

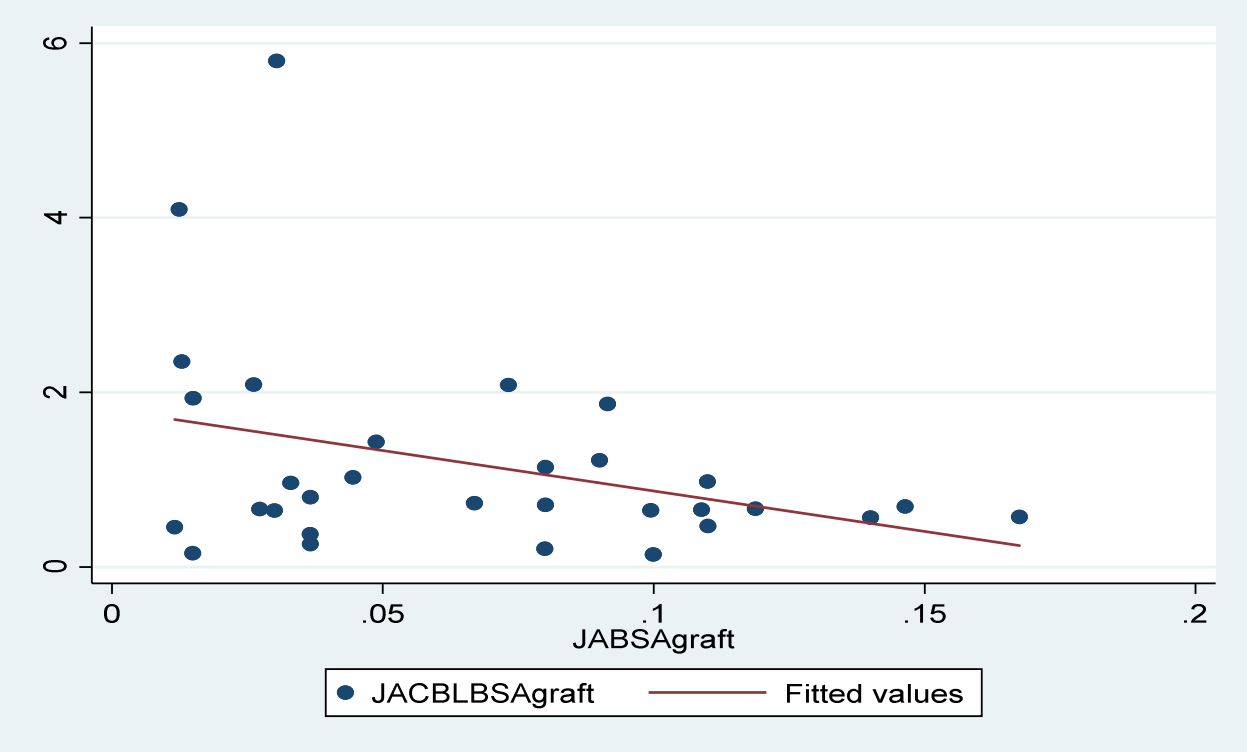
```
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
MD1TBL2c~ |      31    1.174742    .2139011    1.190951    .7378973    1.611586
MD2TBL2c~ |      19    .4577094    .1099479    .4792516    .2267175    .6887012
---------+--------------------------------------------------------------------
combined |      50    .9022694    .1467216    1.037478    .6074213    1.197117
---------+--------------------------------------------------------------------
    diff |            .7170323    .2873402                .1392961    1.294768
------------------------------------------------------------------------------
    diff = mean(MD1TBL2cm2graft) - mean(MD2TBL2cm2graft)          t =   2.4954
Ho: diff = 0                                     degrees of freedom =       48
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9920         Pr(|T| > |t|) = 0.0161          Pr(T > t) = 0.0080
```

Appendix C. Table 4: Initial calculated blood loss summary: Two sample t test with unequal variances, means, standard deviation, and 95% confidence intervals for summarizing calculated blood loss. Mean differences between the methods are also provided.

```
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
MD1TBL2~r |      20    1.107251    .2200433    .9840634    .6466956    1.567807
MD2TBL2~r |      13    .5591966    .1508173    .5437796    .2305939    .8877993
---------+--------------------------------------------------------------------
combined |      33     .891351    .1517389    .8716739    .5822689    1.200433
---------+--------------------------------------------------------------------
    diff |            .5480548    .2997663               -.0633227    1.159432
------------------------------------------------------------------------------
    diff = mean(MD1TBL2cm2OUTgr~r) - mean(MD2TBL2cm2OUTgr~r)        t =   1.8283
Ho: diff = 0                                     degrees of freedom =       31
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9614         Pr(|T| > |t|) = 0.0771          Pr(T > t) = 0.0386
```

```
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
MD1tran~1 |      18         414    111.7882    474.2771    178.1475    649.8525
MD2tran~1 |      13    65.19231    39.21553    141.3936   -20.25098    150.6356
---------+--------------------------------------------------------------------
combined |      31    267.7258    73.19332    407.5231    118.2451    417.2065
---------+--------------------------------------------------------------------
    diff |            348.8077    136.2522                70.14062    627.4748
------------------------------------------------------------------------------
    diff = mean(MD1transub1) - mean(MD2transubgroup1)              t =   2.5600
Ho: diff = 0                                     degrees of freedom =       29
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9920         Pr(|T| > |t|) = 0.0159          Pr(T > t) = 0.0080
```

Appendix C Table 5: Excluded outlier calculated blood loss summary




```
    Source |       SS           df       MS      Number of obs   =        31
-------------+----------------------------------   F(1, 29)        =      3.88
       Model |   5.0241882         1   5.0241882   Prob > F        =    0.0584
    Residual |  37.5267343        29  1.29402532   R-squared       =    0.1181
-------------+----------------------------------   Adj R-squared   =    0.0877
       Total |  42.5509225        30  1.41836408   Root MSE        =    1.1376

------------------------------------------------------------------------------
MD1cblbsagr~t |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  MD1bsagraft |  -9.246646   4.692698    -1.97   0.058    -18.84429    .3510004
       _cons |   1.794897   .3752309     4.78   0.000     1.027464    2.562331
------------------------------------------------------------------------------
Two-sample t test with unequal variances
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
MD1bsag~t |      31    .0670682    .0079489    .0442576    .0508344     .083302
MD2bsag~t |      18    .0502908    .0099429    .0421841    .0293132    .0712685
---------+--------------------------------------------------------------------
combined |      49    .0609051    .0062617    .0438318    .0483151    .0734951
---------+--------------------------------------------------------------------
    diff |            .0167774    .0127297               -.0090134    .0425681
------------------------------------------------------------------------------
    diff = mean(MD1bsagraft) - mean(MD2bsagraft)                  t =   1.3180
Ho: diff = 0                     Satterthwaite's degrees of freedom =  37.0894

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9022         Pr(|T| > |t|) = 0.1956          Pr(T > t) = 0.0978
```

Appendix C. Table 6: Regression analysis for percent BSA grafted and two sample t test.

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23. Critical Care and Anesthetic Care of Military Burn Casualties at Role 3 Facilities CHRISTOPHER V. MAANI, MD*; MICHAEL K. TIGER, MD† ; and JACOB J. HANSEN, DO