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Mild hypothermia is associated with improved outcomes in patients undergoing microvascular head and neck reconstruction

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ABSTRACT

Objective: Microvascular free tissue transfer has become the standard for reconstruction for large defects. With long operative times and an increased surface area exposed, transient hypothermia is common, but it is unclear how this impacts surgical outcomes. This study evaluated the impact of core body temperature on free tissue flap outcomes in patients undergoing microvascular reconstruction.
Study design: Retrospective data analysis.
Setting: Mount Sinai Hospital; NYC, NY; 2007–2016.
Subjects and methods: Demographic information, mean/minimum/maximum body temperatures, and the presence of flap complications (venous thrombosis, arterial insufficiency, flap death, wound infection/dehiscence, fistula, chyle leak, hematoma/seroma) of 519 free tissue transfer patients were documented. Binomial logistic regression was used to examine associations between the presence of flap complications and mean temperature. Statistical analysis used SPSS, with p-values ≤ 0.05 deemed statistically significant.
Results: 393 soft-tissue and 125 osteocutaneous flaps were included. 19.8% (n = 103) patients had the presence of ≥ 1 flap complication, while 80.2% (n = 416) did not. Average temperature for all patients was 36.12 ± 0.84 °C, with minimum at 34.43 ± 0.97 °C and maximum at 37.24 ± 1.23 °C. After controlling for several factors including: tumor stage, radiation, diabetes, BMI, age, sex, and flap type, there was a significant association between flap complications and mean intraoperative temperature (Exp(B) = 1.559, p = 0.004).
Conclusion: Higher intraoperative temperatures were associated with worse outcomes. A mild relative hypothermia may improve flap outcomes in this population. This represents the largest study to date evaluating the impact of intraoperative temperature on free tissue transfer outcomes.

1. Introduction

Microvascular free tissue transfer has become the preferred method for restoring form and functionality when reconstructing large tissue defects in the head and neck. However, these procedures are associated with major complications in up to approximately one third of cases [1–5]. Intraoperative hypothermia is also common [6–8]. While surgical patients, in general, are at an increased risk for hypothermia from radiant heat loss and the anesthetic effects on thermal regulation [9], microvascular free tissue transfer in particular increases risk for transient hypothermia due to long operative times and an increased surface area exposure. Despite the known risk for intraoperative hypothermia, it remains unclear how these changes in core temperature impact outcomes of free tissue transfer in this population.

Previous reports on intraoperative hypothermia, defined by the American Society of Anesthesiologists (ASA) as a core body temperature < 36 °C, have associated lower core body temperatures with increased incidence of infections [10–13], impaired wound healing [14], increased blood loss [15,16], and prolonged hospital stay [10]. Indeed, multiple studies examining intraoperative temperature control in head and neck surgeries suggest a protective role for aggressive warming and maintaining normothermic temperatures [6,7,17]. Studies of free flap survival rates in surgeries not specific to head and neck procedures reported decreased flap survival rates in hypothermic patients, potentially due to vasoconstriction [18]. In a retrospective study of 136 head and neck free flaps, early perioperative complications within 3 weeks of surgery were correlated with a core body temperature of < 35°C [7]. Patients with this level of hypothermia had a higher risk of developing postoperative complications such as complete or partial flap loss, hematomas, or surgical site infections (SSI). While the length of hypothermia did not correlate with these complication rates, those patients whose core temperatures fell below 35 °C at any point during the procedure had an increase rate of both infectious and overall complications.

Interestingly, recent reports have disputed these findings [8,19,20]. Studies are suggesting that higher intraoperative temperatures are

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actually correlated with greater SSI rates [19], and that mild hypothermia may in fact be protective both in rodent models [20] and head and neck patients [8], secondary to increased flap patency and decreased venous thrombosis with lower core body temperatures. A study of 212 head and neck free flap reconstructions found that maximum and minimum intraoperative temperatures were significant predictors of free flap thrombosis, with lower temperatures associated with higher rates of flap patency and survival. The authors ultimately suggested an optimal intraoperative core temperature range of 36.0 °C–36.4 °C for patients undergoing free tissue transfer. While informative, this study was limited by sample size, limited variety of flap donor sites, and a variation in core temperature sampling techniques, which could influence the study findings.

Given the lack of evidence-based protocols for optimal intraoperative core temperature and the continued debate over how hypothermia impacts free tissue transfer, we sought to examine the impact of core body temperature on free tissue flap outcomes in a large database of 519 patients undergoing head and neck microvascular reconstruction. Based on recent reports, we hypothesized that lower intraoperative core body temperatures may be protective and improve flap survival outcomes. We anticipated that results from this study would inform the debate of proper intraoperative temperature control in free tissue transfer in head and neck surgeries.

2. Methods

2.1. Protocol approvals

This study was reviewed and approved by the Icahn School of Medicine at Mount Sinai institutional review board (IRB# IF2046268).

2.2. Study design

To address our research aims, we performed a retrospective data analysis of 554 patients who received free tissue transfer at Mount Sinai Hospital between 2007 and 2016. Intraoperative core body temperature was measured from bladder probes which is standard protocol at our institution. Postoperative flap complications were determined by monitoring with physical exam and Doppler flow detection. Study inclusion criteria were that patients underwent a head and neck free tissue transfer procedure, had valid core temperature data recorded for their procedure, and documentation of postoperative flap complications. 28 patients were removed because they did not have valid temperature data, or standard bladder probe monitoring. An additional 7 patients were excluded as they had multiple flap types performed in a single operative encounter. The primary outcome examined was the association of mean intraoperative core temperature with flap complications. Secondary outcomes examined were the association of maximum or minimum temperature with postoperative flap complications.

2.3. Intraoperative anesthesia and temperature control

The Mount Sinai Hospital Department of Anesthesia follows nationally recognized surgical care improvement project (SCIP) guidelines for intraoperative maintenance of temperature. Intraoperative core body temperature was measured from bladder probes. Temperature goals are > 35.5 °C intraoperatively and > 36 °C by time of drop-off in the Post-Anesthesia Care Unit. Bair warmers are normally turned off intraoperatively if patient temperature increases to > 37 °C. Each patient got a standardized anesthetic in this study which was maintenance of general anesthesia with isoflurane.

2.4. Data collection

Demographic information, mean/minimum/maximum core body temperatures, and the presence of flap complications were documented for each patient. Flap complications documented were: venous thrombosis, arterial insufficiency, flap death, wound infection, wound dehiscence, fistula formation, chyle leak, hematoma, and seroma formation. Additional data abstracted from each patient were comorbidities, ASA status, pathologic diagnosis, history of radiation therapy, surgery, neck dissection, or chemotherapy, tumor TNM stage, and free flap donor site.

2.5. Data analysis

All flap complication outcomes were treated as binomial (present or absent) and summarized by frequencies and percentages. Fisher's exact tests were conducted to investigate if the rates of developing complications were significantly different between binomial temperature groups. Binomial logistic regression was used for association of flap complications with temperature variables. Logistic regression analyses were subsequently adjusted to control for age, sex, BMI, diabetes diagnosis, tumor stage, radiation history, and flap type. Total operative time was also correlated with flap outcomes. Temperature cut-point analysis was accomplished with Youden's J statistic (J = sensitivity + specificity − 1) on a receiver operating characteristic (ROC) curve using a publicly available cut-point determination algorithm [21]. Data is presented as mean ± standard deviation (SD) unless otherwise indicated. A $p \leq 0.05$ was considered significant. Retrospective data were collected and stored in Microsoft Excel 2011 (Microsoft Corp, Seattle, WA), and statistical analysis was performed using SPSS (IBM, New York, NY). Graphs were generated with Prism 7 (GraphPad Software, Inc., San Diego, CA).

3. Results

3.1. Patient demographics

519 patients met inclusion criteria with demographics and baseline data summarized in Table 1. Patient distribution of tumor sites is summarized in Table 2. 393 soft-tissue (165 anterolateral thigh, 184 radial free forearm, 10 latissimus dorsi, 13 rectus abdominis, 13

Table 1
Baseline patient data.

Baseline patient data	
Age, years	63.6 ± 13.6
Sex, n (%)	
Female	178 (34.3)
Male	341 (65.7)
BMI	25.5 ± 5.6
Emergency case status, n (%)	0
ASA status, n (%)	
1	5 (1.0)
2	52 (10.0)
3	378 (72.8)
4	84 (16.2)
Disseminated cancer, n (%)	125 (24.1)
Diabetes, n (%)	84 (16.2)
History of smoking, n (%)	289 (55.7)
Current smoker in past year, n (%)	47 (9.1)
Pathology, n (%)	
SCC	411 (79.2)
Salivary	19 (3.7)
Sarcoma	16 (3.1)
Other	73 (14.1)
Stage, n (%)	
Stage 0	43 (8.3)
Stage 1	65 (12.5)
Stage 2	85 (16.4)
Stage 3	98 (18.9)
Stage 4	228 (43.9)
Chemotherapy, n (%)	180 (34.7)
Radiation, n (%)	263 (50.7)

Table 2
Tumor site locations.

Tumor site	n
Lip	8
Anterior tongue	101
Buccal mucosa	16
Base of tongue	38
Parotid	36
Soft palate	10
Hard palate	17
Larynx	44
Paranasal sinus	4
Nasal cavity	13
Hypopharynx	24
Maxilla	55
Mandible	47
Retromolar trigone	20
Alveolus	29
Other	79

serratus anterior, 2 gracilis, 1 groin, 4 supraclavicular free flap, 1 tensor fasciae latae), 125 osteocutaneous (78 fibula, 45 scapula, and 2 iliac crest), and 1 omental free flaps were included in this study.

3.2. Complications and intraoperative temperatures

19.8% (n = 103) patients had the presence of ≥1 flap complication while 80.2% (n = 416) did not. All flap complication rates are presented in Table 3. Average temperature for all patients was 36.12 ± 0.84 °C, with minimum at 34.43 ± 0.97 °C and maximum at 37.24 ± 1.23 °C (see Fig. 1 for temperature distributions).

Univariate logistic regression revealed that higher mean temperatures were associated with increased rates of having any flap complication (Exp(B) = 1.477, p = 0.006), venous thrombosis (Exp(B) = 1.818, p = 0.046), wound infection (Exp(B) = 1.438, p = 0.026), and seroma formation (Exp(B) = 2.841, p = 0.020) (Table 3). After controlling for several factors including tumor stage, radiation, diabetes, BMI, age, sex, and flap type, there was a significant association between flap complications, venous thrombosis, and seroma formation with mean temperature (Table 3). Temperature data in patients with any flap complication, venous thrombosis, or wound infection were further analyzed.

More generally, total operative time was poorly correlated with mean intraoperative temperature (r = 0.114, p = 0.010) and was not associated with increased flap complications (Exp(B) = 1.002, p = 0.041). Additionally, accounting for total anesthesia time in logistic regression analysis did not significantly alter the impact of mean intraoperative temperature on flap complications (Exp(B) = 1.530, p = 0.005), venous thrombosis (Exp(B) = 2.090, p = 0.025), or wound infection (Exp(B) = 1.400, p = 0.053).

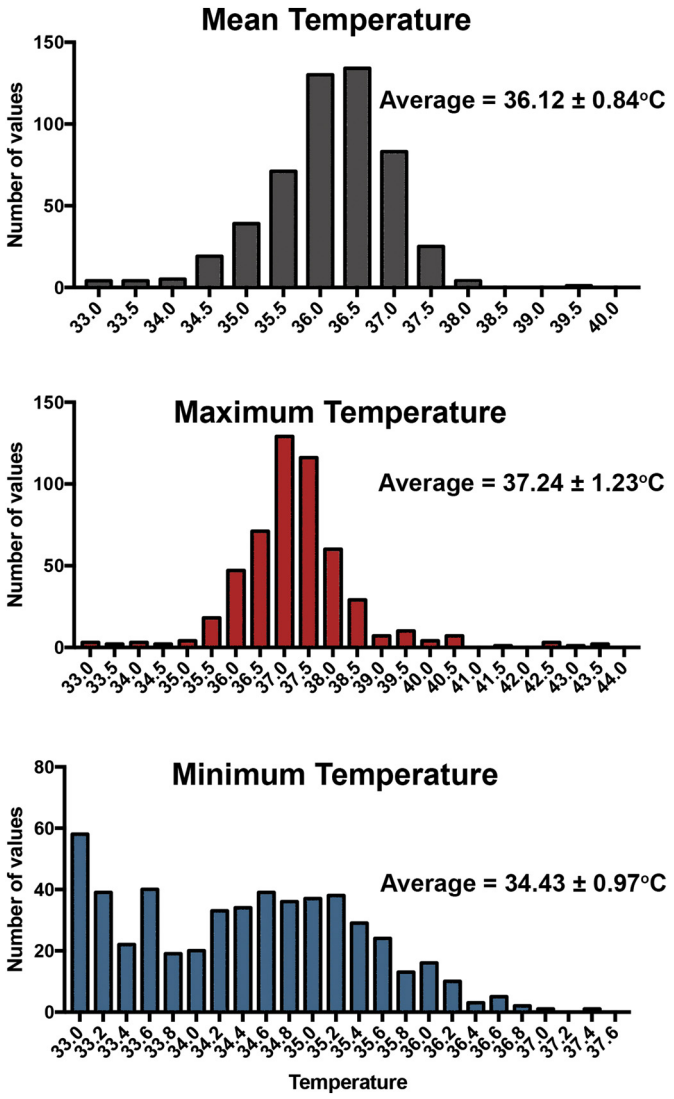

Fig. 1. Temperature distributions. Histograms of mean (top), maximum (middle), and minimum (bottom) intraoperative core body temperatures for 519 patients examined. Mean temperatures for each distribution are included on the corresponding graph.

Subsequent temperature cut-point analysis determined using Youden's J statistic identified a mean temperature cut-off of 36.5 °C, maximum temperature cut-off of 37.6 °C, and minimum temperature of 34.3 °C. Overall flap complication rates for those with mean, maximum,

Table 3
Flap complication rates and impact of temperature.

		Unadjusted		Adjusted	
Complication	n (%)	OR (Exp(B))	p-Value	OR (Exp(B))	p-Value
Any complication	**103 (19.8)**	**1.477 (1.116–1.957)**	**0.006**	**1.559 (1.153–2.107)**	**0.004**
Venous thrombosis	**20 (3.9)**	**1.818 (1.010–3.272)**	**0.046**	**2.108 (1.119–3.974)**	**0.021**
Arterial insufficiency	20 (3.9)	1.112 (0.643–1.924)	0.704	1.203 (0.677–2.135)	0.528
Wound infection	**73 (14.1)**	**1.438 (1.044–1.980)**	**0.026**	1.398 (0.994–1.966)	0.054
Wound dehiscence	39 (7.5)	0.787 (0.543–1.141)	0.206	0.762 (0.506–1.148)	0.193
Fistula	71 (13.7)	1.109 (0.816–1.505)	0.509	1.115 (0.801–1.551)	0.52
Chyle leak	2 (0.4)	0.443 (0.121–1.617)	0.218	1.031 (0.157–6.783)	0.974
Hematoma	38 (7.3)	1.280 (0.844–1.941)	0.245	1.526 (0.976–2.387)	0.064
Seroma	**8 (1.5)**	**2.841 (1.178–6.852)**	**0.020**	**3.251 (1.073–9.848)**	**0.037**
Flap death	27 (5.2)	0.993 (0.625–1.579)	0.978	1.049 (0.636–1.730)	0.852

Bolded items are statistically significant, p < 0.05.

Table 4
Cut-point analysis by Youden's J statistic.

	Complication rates		
	Above temperature (%, n/total)	Below temperature (%, n/total)	p-Value
Mean temp. cut-off 36.5 °C	26.35 (n = 44/167)	16.76 (n = 59/352)	0.013
Min. temp. cut-off 34.3 °C	23.63 (n = 69/292)	14.97 (n = 34/227)	0.015
Max. temp. cut-off 37.6 °C	26.80 (n = 41/153)	16.94 (n = 62/366)	0.015

or minimum temperatures above or below these temperatures are indicated in Table 4. Flap complication rates associated with different temperature cut-offs are shown in Fig. 2. A mean temperature of < 36.5 °C (Exp(B) = 0.543, p = 0.014) with a max temperature < 37.6 °C (Exp(B) = 0.545, p = 0.015) were found to be associated with lower odds of developing flap complications. Mean temperatures below 36.5 °C were not more beneficial (mean < 36.4 °C had Exp(B) = 0.562, p = 0.016 for the development of flap complications; mean < 36.2 °C had Exp(B) = 0.681, p = 0.106), nor were lower maximum temperatures (a maximum temperature < 37.5 °C trended towards decreased flap complication rates, Exp(B) = 0.628, p = 0.058, while temperatures < 37.4 °C were not significantly related to lower flap complication rates (Exp(B) = 0.677, p = 0.108)). Fewer flap complications were associated with a minimum temperature < 34.3 °C (Exp(B) = 0.563, p = 0.018), but not with lower minimum temperatures.

4. Discussion

Here we show that a relative hypothermia may be protective in free flap microvascular head and neck surgery. Results indicate that higher mean, maximum, or minimum temperatures, or simply the presence of higher temperatures, may portend worse outcomes, increasing flap complications overall. Higher temperatures were associated with a greater risk of venous thrombosis, wound infection, and seroma formation. This strong association was maintained after adjusting for confounding factors. In addition, as noted in Table 3, factors which would less likely be expected to be influenced by core temperature such as chyle leak, fistula, or arterial anastomotic failure did not appear to be affected as expected. Our analyses indicate that an intraoperative core body temperature range kept between 34.3 °C–37.6 °C, with a mean temperature approximately 36.5 °C may indeed be protective against specific post-operative flap complications.

While earlier research has suggested that lower intraoperative temperatures are associated with increases in mortality, SSI, ischemic cardiovascular events, blood loss, longer hospital stay [10,22–27], few studies have examined these claims in head and neck surgery, and in particular in head and neck microvascular free tissue transfer with its unique set of considerations. Most reports have looked at intraoperative hypothermia in colorectal or other abdominal procedures such as trauma laparotomy [10,12]. Much of the hypothermia data is also from trauma literature [22,23,25,27]. The few studies that have examined the impact of intraoperative temperature in the head/neck population offer conflicting results. In a study of head and neck surgery, without reconstruction, severe hypothermia (nadir temperatures < 35 °C) was associated with delayed time to extubation, the development of neck seromas, and wound dehiscence [17]. Similarly, a retrospective study of 136 head and neck free flaps found perioperative complications and SSI within 3 weeks of surgery were correlated with the presence of core body temperature of < 35°C [7]. However, this study was limited by a small sample size, and importantly, mean temperatures between patients with complications and those without were not significantly different, nor did the length of hypothermia correlate with complication rates. Similarly, another study of 156 patients found that a nadir temperature < 34.5 °C or mean temperature < 37 °C was correlated with higher post-operative infection rates [6]. However, they found that core temperatures had no association with overall flap failure or pedicle thrombosis. Interestingly while the above temperature cut-offs were correlated with higher SSI rates, mean temperatures < 36.5 °C did not increase infection rates. Other limitations to this study include that it was not specific to head and neck reconstruction (only 32% of patients had head and neck procedures), and 44% of the surgical indications were for reconstruction after trauma or burns. Thus it is difficult to generalize their study to a broader patient population.

Our findings contrast the above reports, and are indeed supported by recent studies that begin to counter this idea that hypothermia heralds worse surgical outcomes [8,19,20]. Evidence shows that mild hypothermia decreases hypoxemia and ischemia in numerous tissues [28]. Additionally, hypothermia may be protective against thrombosis, as multiple reports indicated that platelet and clotting functions may be decreased with hypothermia [15,16,29–33]. Importantly, in contrast to the above studies suggesting that hypothermia is related to higher rates of SSI, a recent report demonstrates that this may not only be the case, but conversely higher intraoperative temperatures may actually be associated with wound infections [19]. Such benefits must be balanced against concerns regarding vasospasm during flap anastomosis at lower temperatures; indeed, we used warm irrigation of the neck after microvascular anastomosis in all cases, regardless of the presence of vasospasm.

A recent study of temperature effects on free tissue transfer [8], albeit not specific to the head and neck, demonstrated that lower temperatures, ranging from 36 °C–36.4 °C, with an optimal temperature of 36.2 °C was associated with decreased flap thrombosis rates. Our study agrees with their suggestions and additionally strengthens it for head and neck microvascular free tissue patients. Our work utilizes a larger sample size, specific to head and neck patients, providing greater

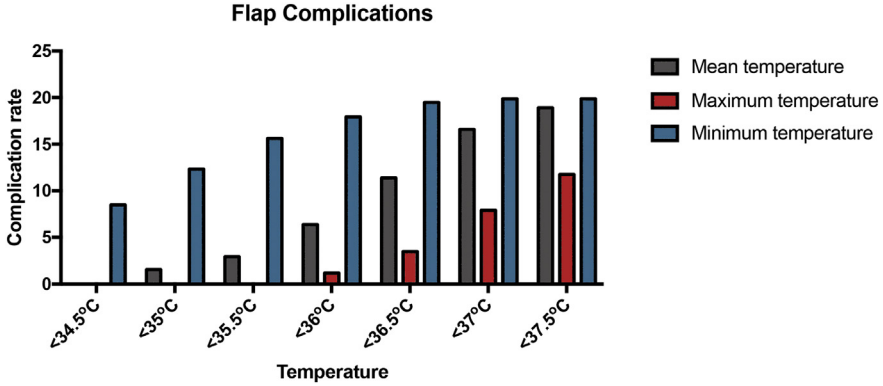

Fig. 2. Flap complication rates. Flap complication rates are indicated for each temperature range. Rates are calculated as a proportion of total sample size (n = 519). Complication rates increase as the temperature cut-off increases.

ability to detect relationships between temperature and various postoperative flap complications. Our study's suggested temperature range is different than the previously "ideal" suggested temperature range, possibly because of the selected methods by which temperature is monitored. The previous investigation measured maximum and minimum operative temperatures for each patient and the temperature was recorded from various sources and post-hoc calibrated to bladder temperatures. Such differences may have impacted the suggested temperature range accounting for the differences in our findings. That said, our suggested range would have to be validated in a prospective study comparing controlled intraoperative temperature ranges to be clinically useful.

It is interesting to note that many of the studies that claim hypothermia is associated with increased SSI or other postoperative complications, tend to use temperatures of < 35 °C as their cut-off and only examined nadir temperatures for the surgery as the primary measure instead of mean core temperature [6,7,10,17]. The definition of hypothermia is often not consistent. While our findings showed that overall, lower temperatures were protective for flap complications and wound infections, our suggested mean intraoperative temperature was > 35 °C—higher than the temperature cut-offs previous reports suggest portend worse outcomes. It is possible that lower temperatures are associated with greater complications overall, but mild hypothermia, or at least avoidance of aggressive warming, may yield better free flap outcomes in particular. Control of intraoperative temperature must balance reduction in flap complications with overall physiologic benefits to the patient.

Our examination is limited by being a single center, retrospective study, and rates of certain flap complications, such as venous thrombosis, are low overall. Thus, a larger sample size is required to more accurately describe temperature relationships to flap outcomes. While these temperature differences are not the sole determining factor for flap complications, and our study's retrospective nature does not allow for the distinction between causation and correlation, our results suggest that temperature may have an important role in free flap outcomes, and that tighter intraoperative temperature regulation may be needed. Despite its limitations, our study informs the discussion regarding proper temperature regulation during microvascular free tissue transfer in head and neck surgery and indicates further work examining temperature control effects in prospective trials are warranted.

5. Conclusion

Higher intraoperative temperatures were associated with worse outcomes. A relative hypothermia may thus improve flap outcomes in this population. This investigation represents the largest study to date evaluating the impact of intraoperative temperature on outcomes for free tissue transfer.

References

[1] Arce K, Moore EJ, Lohse CM, Reiland MD, Yetzer JG, Ettinger KS. The American College of Surgeons National Surgical Quality Improvement Program surgical risk calculator does not accurately predict risk of 30-day complications among patients undergoing microvascular head and neck reconstruction. J Oral Maxillofac Surg 2016;74:1850–8. Elsevier.

[2] Borggreven PA, Kuik DJ, Quak JJ, de Bree R, Snow GB, Leemans CR. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction. Head Neck 2003;25:808–15. Wiley Subscription Services, Inc., A Wiley Company.

[3] Ryan MW, Hochman M. Length of stay after free flap reconstruction of the head and neck. Laryngoscope. 110. John Wiley & Sons, Inc.; 2000. p. 210.

[4] Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg 1999;103(2):403–11.

[5] Suh JD, Sercarz JA, Abemayor E, et al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg Vol 130: American Medical Association; 2004: 962–966.

[6] Hill JB, Sexton KW, Bartlett EL, et al. The clinical role of intraoperative core temperature in free tissue transfer. Ann Plast Surg 2015;75:620–4.

[7] Sumer BD, Myers LL, Leach J, Truelson JM. Correlation between intraoperative hypothermia and perioperative morbidity in patients with head and neck cancer. Arch. Otolaryngol. Head Neck Surg 2009;135:682–6. [American Medical Association].

[8] Liu Y-J, Hirsch BP, Shah AA, Reid MA, Thomson JG. Mild intraoperative hypothermia reduces free tissue transfer thrombosis. J Reconstr Microsurg 2011;27:121–6.

[9] Young VL, Watson ME. Prevention of perioperative hypothermia in plastic surgery. Aesthet Surg J 2006;26:551–71.

[10] Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med, 334. 1996. p. 1209–15.

[11] Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. Lancet 2001;358:876–80.

[12] Seamon MJ, Wobb J, Gaughan JP, Kulp H, Kamel I, Dempsey DT. The effects of intraoperative hypothermia on surgical site infection: an analysis of 524 trauma laparotomies. Ann Surg 2012;255:789–95.

[13] Beilin B, Shavit Y, Razumovsky J, Wolloch Y, Zeidel A, Bessler H. Effects of mild perioperative hypothermia on cellular immune responses. Anesthesiology 1998;89:1133–40.

[14] Esclamado RM, Damiano GA, Cummings CW. Effect of local hypothermia on early wound repair. Arch Otolaryngol Head Neck Surg 1990;116:803–8.

[15] Kahn HA, Faust GR, Richard R, Tedesco R, Cohen JR. Hypothermia and bleeding during abdominal aortic aneurysm repair. Ann Vasc Surg 1994;8:6–9.

[16] Bernabei AF, Levison MA, Bender JS. The effects of hypothermia and injury severity on blood loss during trauma laparotomy. J Trauma 1992;33:835–9.

[17] Agrawal N, Sewell DA, Griswold ME, Frank SM, Hessel TW, Eisele DW. Hypothermia during head and neck surgery. Laryngoscope 2003;113:1278–82. John Wiley & Sons, Inc.

[18] Lee L-I, Lin C-C, Chen M-C, Lin C-H, Shyr M-H. Anesthesia duration and hypothermia affect graft survival in vascularized free flap surgery. Tzu Chi Med J 2005;17:17–20.

[19] Brown MJ, Curry TB, Hyder JA, et al. Intraoperative hypothermia and surgical site infections in patients with class I/clean wounds: a case-control study. J Am Coll Surg 2017;224:160–71.

[20] Thomson JG, Mine R, Shah A, et al. The effect of core temperature on the success of free tissue transfer. J Reconstr Microsurg 2009;25:411–6.

[21] Budczies J, Klauschen F, Sinn BV, et al. Cutoff finder: a comprehensive and straightforward web application enabling rapid biomarker cutoff optimization. PLoS One. Vol 72012: e51862.

[22] Aitken LM, Hendrikz JK, Dulhunty JM, Rudd MJ. Hypothermia and associated outcomes in seriously injured trauma patients in a predominantly sub-tropical climate. Resuscitation 2009;80:217–23.

[23] Frank SM, Beattie C, Christopherson R, et al. Unintentional hypothermia is associated with postoperative Myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology, 78. 1993. p. 468–76.

[24] Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. JAMA, 277. 1997. p. 1127–34.

[25] Martin RS, Kilgo PD, Miller PR, Hoth JJ, Meredith JW, Chang MC. Injury-associated hypothermia: an analysis of the 2004 National Trauma Data Bank. Shock 2005;24:114–8.

[26] Schmied H, Reiter A, Kurz A, Sessler DI, Kozek S. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet 1996;347:289–92.

[27] Wang HE, Callaway CW, Peitzman AB, Tisherman SA. Admission hypothermia and outcome after major trauma. Crit Care Med 2005;33:1296–301.

[28] Doufas AG, Sessler DI. Physiology and clinical relevance of induced hypothermia. Neurocrit Care 2004;1:489–98. Humana Press.

[29] Hess JR, Brohi K, Dutton RP, et al. The Coagulopathy of trauma: a review of mechanisms. J Trauma Acute Care Surg 2008;65:748–54.

[30] Kermode JC, Zheng Q, Milner EP. Marked temperature dependence of the platelet calcium signal induced by human von Willebrand factor. Blood 1999;94:199–207.

[31] Reed RL, Bracey AW, Hudson JD, Miller TA, Fischer RP. Hypothermia and blood coagulation: dissociation between enzyme activity and clotting factor levels. Circ Shock 1990;32:141–52.

[32] Valeri CR, MacGregor H, Cassidy G, Tinney R, Pompei F. Effects of temperature on bleeding time and clotting time in normal male and female volunteers. Crit Care Med 1995;23:698–704.

[33] Wolberg AS, Meng ZH, Monroe DM, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004;56:1221–8.