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Perioperative warming, oxygen, and Ilomedin on oxygenation and healing in infrainguinal bypass surgery

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ABSTRACT

Background: Perioperative adjuncts are utilized across surgical specialities with the goal of improving patient outcomes. High-dose oxygen and extended warming are shown to increase wound collagen deposition during abdominal surgery. Prostacyclin is shown to improve limb salvage and patency rate in infrainguinal bypass (IIB) surgery. This study evaluated the impact of these adjuncts on healing and perfusion post IIB surgery.

Methods: This randomized controlled study allocated patients undergoing IIB surgery into three treatment arms (perioperative high-dose oxygen, extended warming, and a synthetic prostacyclin) or a control group. The primary outcome was accumulation of hydroxyproline (OHP, collagen surrogate marker) as collected in polytetrafluoroethylene implants on day 5. Secondary outcomes included levels of growth factors and cytokines, and tissue oxygenation of the wound and foot as measured by hyperspectral technology and ankle-brachial pressure index. Clinical outcomes were observed to day 30, with long-term follow-up of 12 mo.

Results: Seventy-one patients completed the study. Comparing treatment groups with the control at day 5, there were no differences in OHP, growth factors or cytokines levels, or improvement in tissue oxygenation at the surgical incision. However, there was more flow to the foot (HT-SUM (%) change) in the Ilomedin group compared to control (0% *versus* −14.6%, $P = 0.045$). HT-deoxy was higher at the peripheries in the oxygen and temperature groups, suggesting decreased tissue oxygenation.

Conclusions: The perioperative treatments did not dramatically improve oxygenation or healing of the surgical wound in IIB surgery; however, Ilomedin may result in greater flow to the peripheries.

Introduction

Optimizing tissue perfusion is a key component of wound healing, especially in compromised patients with comorbidities that influence healing such as peripheral vascular disease and diabetes. Surgical wound complications following infrainguinal bypass (IIB) surgery can be up to 40% and can render the revascularization procedure a failure.[1] Previous studies have

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suggested that peripheral vascular perfusion can be enhanced perioperatively by supplemental oxygen, administration of a vasodilator drug, such as Ilomedin (synthetic prostacyclin analogue), or by active warming to enrich thermoregulation by vasodilation.[2-5] The effects of these adjuncts on wound healing and tissue oxygenation in IIB among vascular patients are unknown.

The aims of this study were to examine the roles of key molecular markers in wound healing, namely hydroxyproline (OHP) and growth factors during vascular surgery. In addition, to determine how these markers and peripheral tissue oxygenation were influenced by thermal or chemical vasodilation, and oxygen.

The primary end point was wound healing, assessed by incorporation of OHP into embedded polytetrafluoroethylene (PTFE) implants. Secondary end points included analyses of growth factors in the wound tissue and tissue oxygenation. The hypothesis was that perioperative high-dose oxygen, extended warming, and perioperative Ilomedin would improve tissue oxygenation and wound healing during IIB surgery.

Methods

The protocol and informed consent for this randomized control study was approved by the local Northern Y ethics committee (NTY/08/04/032), and all participants gave informed consent.

Eligibility

Patients undergoing IIB surgery at Waikato Hospital, Hamilton, New Zealand from January 2009 to July 2011 were considered for inclusion. Patients were excluded if they had untreated critically stenotic lesions proximally (e.g., aortoiliac segment), chronic obstructive pulmonary disease with retention of carbon dioxide, previous exposure to bleomycin, use of Ilomedin, corticosteroids, or immunosuppressant's 4 wk before surgery, sensitivity to Ilomedin, or a history of methicillin-resistant *Staphylococcus aureus*.

Randomization methods

Participants were randomly allocated into four groups:

- Oxygen group (FiO_2 80% without extended warming and Ilomedin)
- Temperature group (FiO_2 30% with preoperative and postoperative warming using Bair Hugger and without Ilomedin)
- Ilomedin group (FiO_2 30% with Ilomedin injected intra-arterially intraoperatively and one single dose immediately postoperatively, without extended warming)
- Control group (FiO_2 30% without extended warming or Ilomedin)

Participants were blinded as to their group allocation, although concealment was difficult for the temperature group. Randomization codes were formulated by Statistical Package for the Social Sciences software (SPSS, version 22 [IBM Corporation, Armonk, NY, USA]) on a 1:1 basis. The results were placed in an envelope, which was opened by the anesthetist at least 2 h before induction of anesthesia.

Power calculation

A minimum of 76 patients were required, with 19 participants in each group, to detect a mean increase of 0.075-μg OHP per cm tubing at day 5 in each treatment group compared with controls with a power of 80% and a significance level of 5%. A 25% absolute increment in OHP content was deemed to be clinically significant.

Number of participants

One hundred and five patients underwent IIB involving a medial calf incision during the recruitment period. Eighty-five were invited to participate after considering the inclusion and exclusion criteria (Fig. 1). Eighty patients were consented for the study; however, nine patients were further excluded during the study. Three did not have successful IIB during surgery, three had revisions of the bypass graft before day 5, and two patients violated protocol (had higher FiO_2 than prescribed by the study). One patient allocated to the oxygen group had a cardiac arrest and died on day 1. No participation was terminated as a result of complications during the study.

Seventy-one patients completed the study on day 5 when the PTFE implant was removed to evaluate the primary outcome. Recruitment was slower than predicted.

Study design

After the collection of demographic data, the number of patent crural vessels, or "run-offs", was determined. This preoperative imaging utilized digital subtraction arteriography as preferred imaging, or magnetic resonance angiography, computed tomographic angiography, and arterial duplex scan if no superior modality was available. Patients were scored out of 3, with a score of 1 allocated per patent crural vessel without critical stenosis; 0.5 per vessel with one or more critical stenosis; and zero per vessel with any length of chronic total occlusion regardless of the presence of collateral flow.

At least 2 h before surgery, under standardized conditions, the ankle-brachial pressure index (ABI) was recorded by handheld Doppler, and transcutaneous tissue oxygenation was quantified using the OxyVu (HyperMed Inc, Boston, MA). This device utilizes hyperspectral technology and was validated by the author previously. The locations for repeat measurement were the medial aspect of the knee where the skin incision would lie, and the plantar foot over the head of the first metatarsal. OxyVu yielded oxygen saturation (HT-sat, %), oxyhemoglobin (HT-oxy), and deoxyhemoglobin (HT-deoxy) in arbitrary units (AU) and skin temperature in degrees Celsius. HT-sum (sum of HT-oxy and HT-deoxy) quantified the amount of hemoglobin at the skin capillaries.

Each patient was given chlorhexidine and alcohol (Chloraprep) for skin preparation and a standard protocol for antibiotic prophylaxis on induction. Antibiotics continued for 24 h (1-g cefazolin intravenously or erythromycin if

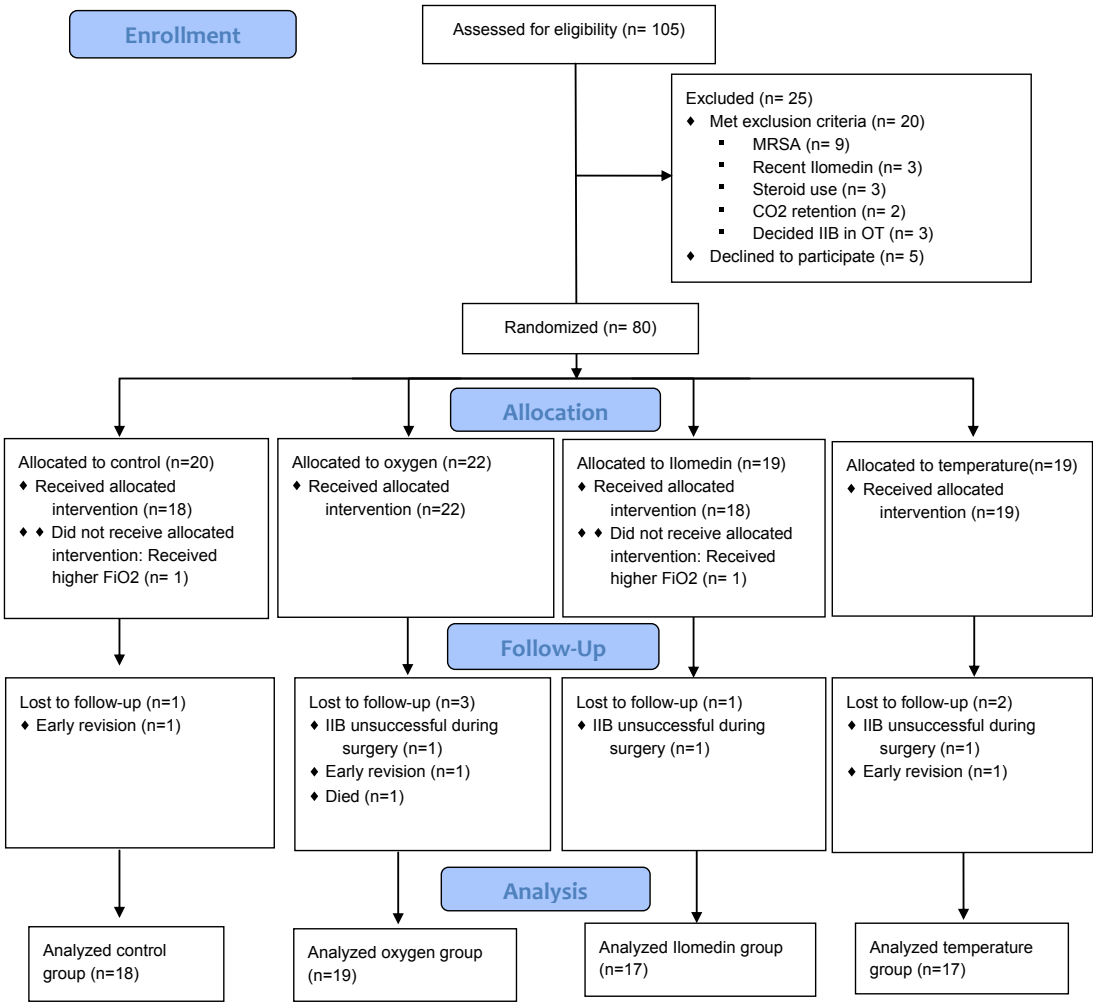

Fig. 1 – Flow diagram showing patient recruitment. (Color version of figure is available online.)

contraindicated). Surgery was performed in the manner preferred by the individual treating surgeon, and corticosteroids were not administered. All patients received forced-air warming device at 38°C intraoperatively irrespective of allocation group. Ambient temperature was set at 21°C, and all intravenous fluids were warmed.

For patients in the temperature group, a forced-air warming device (Bair Hugger) was placed on the patients and set at 38°C for 2 h before induction of anesthesia, during surgery and for 2 h postsurgery with the aim to raise core temperature. Core temperatures were monitored before, immediately after, and every 30 min following surgery for 2 h using a tympanic thermometer. Intraoperative temperatures were recorded every 30 min during anesthesia using a nasopharyngeal temperature probe. If core temperature exceeded 38°C during surgery, the Bair Hugger would be turned down.

For the oxygen group, FiO_2 was set to 80% and maintained throughout surgery, whereas other groups received 30%. During the first 2 h postoperatively, FiO_2 was maintained at 30% or 80% according to randomization. Patients requiring changes in FiO_2 greater than 10% from the study protocol intraoperatively to maintain oxygen saturation were also excluded.

In the Ilomedin group, 50 μg of Ilomedin was prepared with 250 mL of saline; thereafter, 3000 ng of Ilomedin in 15 mL was slowly infused endoluminally into the bypass graft intraoperatively using an 18-gauge cannula once the anastomoses of the graft were completed. The remaining Ilomedin was infused intravenously immediately postoperatively at a rate of 10-40 mL/h for 6 h as per unit protocol with blood pressure monitoring.

Before skin closure, a PTFE tube (Maquet, Hudson, NH) 5 cm in length, 2 mm in diameter, and 1 mm in thickness with a pore size of 60 μM and a 1 cm^3 cubed-shaped viscose cellular sponge (PVA Unlimited, Warsaw, Indiana) were implanted entirely subcutaneously parallel to the wound incision with the proximal end flush with the skin. The location was standardized at the incision close to the knee. A 3/0 nylon suture was placed in one end of the implant as a locator. Another 3/0 nylon stitch was secured just beneath the skin incision to cover the end of the tube with surrounding skin to minimize infection.

On day 5, embedded implants were harvested using sterile technique under topical anesthesia (Emla 5% cream). Once extracted, tubes were transferred to a sterile pot and immediately stored at below −80°C in the laboratory at Waikato Hospital. The content of OHP (expressed in μg/cm of tube) was

quantified using spectrometry with protocol based on key-validated OHP studies.[6,7] Day 5 was chosen to balance the risk of wound complications or graft infections, and the benefit of accumulating more OHP.[8]

Wound fluid from the saturated polyvinyl alcohol foam sponge collected on day 5 from the knee wound was analyzed for growth factors (transforming growth factor-β1, vascular endotheial growth factor, fibroblast growth factor-2, tumor necrosis factor-α, and interleukin-8) using Milliplex and enzyme-linked immunosorbant assay (ELISA) technique.[9]

Tissue oxygenation was measured using OxyVu on days 1 and 3 postoperatively. A detailed scan using OxyVu and calculation of ABI were performed on days 5. Surgical wounds were assessed for complications with a follow-up appointment on day 14 and 30. Long-term outcomes of patency, limb salvage, and survival were observed for at least 12 mo.

Statistical analysis

Data was collected in Excel. Statistical analyses were performed using SPSS. A type I error of 5% ($P \leq 0.05$, two-tailed) was statistically significant.

Descriptive statistics were described in terms of the range, mean or median, and SD. When comparing the means of two groups of continuous variables, parametric analysis (Student's *t*-test) was used. In the setting of comparing means for discrete variables, chi-squared and Fisher's exact tests were applied depending on the size of the sample. Pearson's correlation was used to test for an association between continuous variables. Bonferroni correction was applied where there were multiple hypotheses with three comparison groups (i.e., three treatment arms and one control). Analysis of variance (two-way repeated measures) or the Kruskal-Wallis test was used to compare the means of more than two groups. The latter was used to detect differences in basic demographics between the groups. Primary and secondary patency rates, limb salvage rates, and mortality rates were determined using Kaplan-Meier survival analysis.

Results

There were no differences in basic demographics among the four groups (Table 1). Twenty-four patients (34%) had diabetes, and fifty-five (77%) patients had rest pain or ulcers. Twenty-eight patients had previous lower limb bypasses, 16 of which were for the diseased limb.

Table 2 demonstrates that there were no significant differences in operative findings between the groups. The most common site of proximal anastomosis was the common femoral artery (79%), whereas the below knee popliteal artery

Table 1 – Basic demographics of study participants.

Group	Control	Oxygen	Ilomedin	Temperature	P value
Patients	18	19	17	17	0.99
Male	11	14	10	12	0.74
Mean age (SD)	71 (10.7)	69 (9.1)	67 (11.5)	74 (8.2)	0.19
Caucasian	15	15	15	17	0.32
BMI (SD)	26 (6)	27 (4)	27 (4)	27 (4)	0.96
Acute presentation	8	5	6	3	0.35
Claudication	5	6	2	3	0.77
Rest pain	4	7	8	5	
Tissue loss	9	6	7	9	
Ipsilateral local infection	4	3	3	2	
Smoker	4	2	5	3	0.89
Ex-smoker	12	15	10	12	
Pack-years (SD)	36 (37)	30 (29)	45 (37)	44 (38)	0.62
Diabetic	8	7	5	4	0.59
IDDM	5	4	2	2	0.74
Previous angioplasty	10	10	6	9	0.62
Previous BPG	6	8	8	6	0.83
Previous BPG (ipsilateral)	5	3	5	3	0.69
Renal impairment	4	4	1	3	0.58
ESRF	0	2	0	1	
Hypertension	13	18	13	15	0.20
Dyslipidemia	13	16	11	12	0.56
IHD	8	8	6	12	0.18
COPD	4	2	1	1	0.37

BPG = bypass graft; COPD = chronic obstructive pulmonary disease; ESRF = end-stage renal failure; IDDM = insulin-dependent diabetes mellitus; IHD = ischemic heart disease.

Table 2 – Operative findings of the participants.

Group	Control	Oxygen	Ilomedin	Temp	P value
V-POSSUM					
PS (SD)	22 (6)	22 (8)	22 (5)	24 (7)	0.83
OS (SD)	11 (2)	11 (2)	10 (1)	11 (2)	0.76
Run-offs					
(SD)	1.6 (0.7)	2.1 (0.9)	1.9 (0.8)	1.9 (0.7)	0.22
Operation time (min)					
Min (SD)	235 (62)	214 (56)	224 (79)	243 (89)	0.64
GA	18	17	16	17	0.56
Inflow					
Ext iliac	0	2	1	0	0.40
CFA	16	13	13	14	
SFA	2	2	2	2	
PFA	0	0	1	0	
GSV BPG	0	2	0	1	
Outflow					
AK pop	2	3	2	2	0.52
BK pop	13	10	11	12	
At	0	2	0	1	
TPT	0	1	1	0	
PT	2	0	3	1	
Peroneal	1	0	0	1	
GSV BPG	0	2	0	0	
Conduit					
GSV	8	10	7	9	0.31
Cephalic	3	1	0	1	
Basilic	0	0	0	2	
Composite	1	0	1	0	
PTFE + Miller	6	8	9	5	
Arterial pO2					
mmHg (SD)	115 (32)	249 (64)	120 (29)	103 (22)	0.0001
Temp °C (SD)					
At incision	35.9 (0.4)	36.0 (0.5)	36.2 (0.5)	36.2 (0.4)	0.28
Postoperative	36.7 (0.7)	36.6 (0.5)	36.6 (0.4)	37.1 (0.9)	0.09
2-h postoperative	36.4 (0.6)	36.4 (0.7)	36.6 (0.4)	36.6 (0.5)	0.41

V-POSSUM = Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; PS = physiological score; OS = operative score; GA = general anesthesia; Ext iliac = external iliac; CFA = common femoral artery; SFA = superficial femoral artery; PFA = profunda femoris artery; GSV BPG = great saphenous vein bypass graft; AK = above knee popliteal artery; BK = pop, below knee popliteal artery; At = anterior tibial artery; TPT = tibial-peroneal trunk; PT = posterior tibial artery; GSV = great saphenous vein.

was the most common outflow vessel (65%). The great saphenous vein was the preferred bypass conduit (48%), while 28 (39%) of patients had PTFE as a bypass conduit. In these settings, a Miller cuff with a vein was routinely formed at the distal end.

Effects of oxygen and active warming

The arterial partial pressure of oxygen (paO_2) from arterial blood gas samples was significantly higher in the oxygen group than that in the other 3 groups (Table 3; $P = 0.0001$).

Core temperature increased with active warming in the first 90 min. This decreased by the time of knife-to-skin despite receiving active warming throughout the transit from the ward to the preoperative bay and theater (Fig. 2). The drop in core temperature between 90 and 120 min was possibly due to an interruption from transferring onto a cooler operating table, a change to the cooler ambient temperature of the operating theatre, or side effects of anesthetic agents. Active warming 2 h before surgery in the temperature group had a minor but significant effect on core temperature (36.1°C at application of Bair Hugger, 36.2°C at knife-to-skin; $P \leq 0.01$). Prewarming and postwarming did not have an effect on core temperature at skin incision or after surgery, although the patients in the temperature group appeared to have a higher core temperature immediately following surgery ($P = 0.09$; Table 3).

Table 3 – Influence of supplemental oxygen and active warming on arterial oxygenation and core temperature.

Group	Control	Oxygen	Ilomedin	Temp	P value
Arterial pO_2					
mmHg (SD)	115 (32)	249 (64)	120 (29)	103 (22)	0.0001
Mean core temperature °C (SD)					
At incision	35.9 (0.4)	36.0 (0.5)	36.2 (0.5)	36.2 (0.4)	0.28
After surgery	36.7 (0.7)	36.6 (0.5)	36.6 (0.4)	37.1 (0.9)	0.09
2 h after surgery	36.4 (0.6)	36.4 (0.7)	36.6 (0.4)	36.6 (0.5)	0.41

Accumulation of hydroxyproline

There were no significant differences in the primary outcome of OHP accumulation on day 5 when each treatment arm was compared with the control group (Table 4). Accumulation of OHP did not correlate with intraoperative PaO_2 ($P = 0.84$), core temperature at skin incision ($P = 0.19$), or core temperature at 2 h after surgery ($P = 0.9$).

Growth factors

In congruence with the primary outcome, there was no difference in the levels of biochemical markers examined when the treatment arms were compared with the control group (Table 4). Fibroblast growth factor-2 was the only growth factor that correlated with OHP, with a Pearson's correlation coefficient (r) 0.38 ($P = 0.001$). Transforming growth factor-β1 correlated with fibroblast growth factor-2 ($r = 0.49$; $P < 0.0001$).

Assessment of tissue oxygenation

The average of the six sites tested around the PTFE implant was used to determine periwound oxygenation. When studying the entire cohort, the HT-sat of the wound at day 5 was compared with the baseline HT-sat before surgery to provide a ratio. The mean of this ratio was 1.51, implying that the saturation of oxyhemoglobin increased by 51% on day 5 after surgery. In fact, the ratio for HT-sat was 1.67 on day 1; and similarly, the ratio for HT-sum was 1.52 on day 3 and 1.47 on day 5.

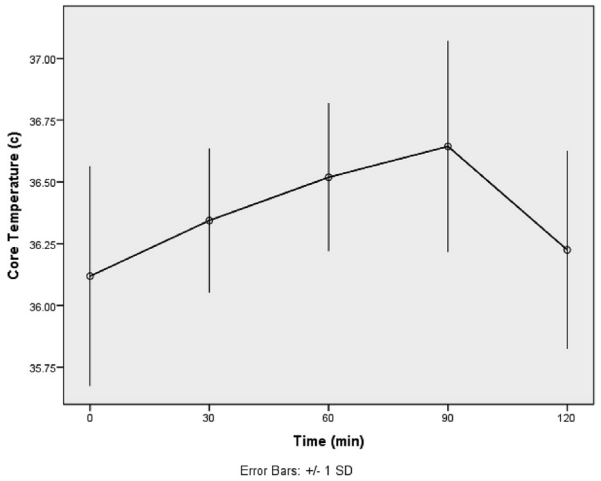

Fig. 2 – Changes in core temperature measured at 30-minute intervals using a tympanic thermometer in the 17 patients within the active warming intervention group during the 2 h of preoperative warming with Bair Hugger set to 38°C.

HT-sat of the peripheral blood flow of the diseased foot in all the patients at day 5 was also assessed. HT-sat increased by 4.8% by day 5 relative to prior surgery. The ABI of the diseased foot increased by 94% by day 5.

When changes in transcutaneous oxygenation at the foot in each treatment group were compared with the control group, there were several statistical differences (Table 5). Care should be taken when interpreting these P values, as this study failed to meet the primary outcome. On day 5, there was more flow (HT-SUM % change) to the foot in the Ilomedin group compared to control (0% *versus* −14.6%, $P = 0.045$). Decrements in HT-deoxy postoperatively were less than hypothesized in the oxygen and temperature groups, affecting the HT-sat. This suggests decreased tissue oxygenation when compared to the control.

Accumulation of OHP was not influenced by transcutaneous oxygenation at the surgical incision site ($P = 0.34$).

Clinical outcomes

There was no difference in prevalence of complications between the treatment arms and the control group within the first 30 days (Table 6; P values not shown). Surgical site infections (SSIs) occurred at 39.4% across all participants, with major SSI affecting 7%. SSIs were defined by Centres for Disease Control and Prevention (CDC) criteria. Major SSI and major dehiscence were defined as requiring hospitalization for intravenous antibiotics or surgical intervention. One patient in the oxygen group had a PTFE bypass graft explanted within 30 d secondary to graft infection originated from the groin.

Patients were followed for a period of 12 mo (Table 7). Overall primary and secondary patency rates at 12 mo were 53% and 67%, respectively, whereas the limb salvage rate at 12 mo was 86%. There was no significance in these rates between the treatment arms and the control group (P values not shown).

Discussion

Despite evidence of the beneficial effects of high-dose oxygen and active warming on wound healing in abdominal surgery,

Table 4 – Levels of hydroxyproline and various growth factors in samples taken from each participant in each of the three treatment groups and the control group as measured on day 5.

Marker	Control	Oxygen	Ilomedin	Temp
OHP μg/cm (SD, *P*-value)	2.39 (2.26)	1.73 (0.99, 0.27)	2.19 (1.62, 0.77)	1.59 (0.72, 0.16)
TGF-β ng/mL (SD, *P*-value)	0.25 (0.33)	0.29 (0.21, 0.71)	0.24 (0.16, 0.91)	0.26 (0.31, 0.98)
FGF-2 ng/mL (SD, *P*-value)	0.70 (1.6)	0.40 (0.45, 0.46)	0.35 (0.28, 0.39)	0.31 (0.22, 0.33)
VEGF ng/mL (SD, *P*-value)	2.63 (1.37)	2.43 (2.06, 0.74)	2.58 (1.45, 0.93)	2.84 (1.92, 0.72)
TNF-α pg/mL (SD, *P*-value)	30.0 (22.5)	56.3 (80.6, 0.21)	33.1 (22.3, 0.67)	45.2 (35.2, 0.15)
IL-8 ng/mL (SD, *P*-value)	22.7 (15.4)	16.4 (7.5, 0.13)	17.5 (11.4, 0.26)	32.6 (34.7, 0.31)

FGF-2 = fibroblast growth factor-2; VEG = vascular endothelial growth factor; TNF-α = tumor necrosis factor alpha; IL-8 = interleukin-8.

no such evidence was found for patients with peripheral vascular disease undergoing IIB. Potential theories for this require further examination, including a difference in microcirculation and endothelial injury between vascular and nonvascular patients; and differences in heat redistribution between central and peripheral compartments.

More than 60 published wound healing studies have used OHP for histological assessment of granulation tissues and study of collagen synthesis.[6] OHP is an amino acid confined exclusively to collagen, connective tissue selenoproteins, and elastin. It is considered a reliable surrogate marker of wound healing.[10-12]

Goodson and Hunt[13] described a technique in which a PTFE tube was implanted subcutaneously. Over time, granulation tissue was deposited within the tube. Once removed, OHP was quantified using spectrophotometry.[14] Their study of 40 implants in 30 healthy participants demonstrated reliability and reproducibility of this method. Accumulation of OHP was found to start as early as 8 h and increased slowly over 5 d. After day 5, it increased exponentially. At day 5, there was significant accumulation of OHP, and the standard deviation (SD) was the smallest (0.30 ± 0.08 μg OHP per cm tubing) when compared with day 7 and beyond.[13] Hence, day 5 was chosen for PTFE tube removal in this study. This method provided only one snapshot of the wound healing process, comprising mostly of the inflammatory phase. The effects of the adjuncts studied may be significant later in the proliferative phase, when there may be a higher type I to type III collagen ratio. However, the delayed removal of PTFE implants may also increase the risk of infection.

A focus of this study examined whether the adjuncts of oxygen, temperature, and Ilomedin impacted on tissue oxygenation specifically. These results allowed a review of the known relationship between tissue oxygenation and accumulation of OHP (as a marker of wound healing). Hyperspectral imaging (via OxyVu) was utilized as a suitable, validated technology that is capable of analyzing tissue perfusion.[15,16]

As a result of surgery, wound oxygenation and blood flow to the foot improved; however, the adjuncts of temperature, oxygen, and Ilomedin do not appear to have provided dramatic additional benefit in terms of OHP accumulation or tissue oxygenation.

Even with a higher circulating paO_2 in the oxygen group during surgery, intraoperative arterial clamping may have prevented increased oxygen levels reaching the surgical wounds. In addition, the warmed blood and intravenous fluid may not have reached the lower limb during clamping. Perhaps the hypothesis of this study might have been confirmed in other vascular procedures that also mandate optimal wound healing, such as major and distal amputations, which do not require arterial clamping to the wounds.

It is important to note that the half-life of Ilomedin is 20-30 min[17]; hence, a single dose intraoperatively followed by a 6-h course immediately postoperatively might not be sufficient to effect oxygenation at day 5. Nevertheless, blood flow in the foot appeared to be enhanced by the effect of Ilomedin even on day 5. An improvement in flow to the peripheries was not recorded for the oxygen or temperature groups. In contrast, there were suggestions of decreased oxygenation in these 2 groups compared to the controls.

Furthermore, BairHuggers were placed on all patients intraoperatively over the central compartment, while the lower limbs were exposed. Heat loss is significant in the

Table 5 – Summary of statistically significant changes in OxyVu readings in treatment arms *versus* the control group.

Variables	Group	Day	Treatment arm (%)	Control (%)	*P* value
HT-deoxy	Oxygen	5	0	−18.1	0.037
HT-sum	Ilomedin	5	0	−14.6	0.045
HT-deoxy	Temperature	5	−2.2	−12.2	0.039
HT-sat	Temperature	1	−1.4	10.0	0.044
		3	−1.9	8.3	0.050
		5	−7.7	5.3	0.04

Table 6 – Number of wound and systemic complications observed within the first 30 d after surgery, showing the percentage of participants affected in each treatment arm.

Group	Control	Oxygen	Ilomedin	Temp
SSI (%)	7 (38.9)	6 (31.6)	6 (35.3)	8 (47.1)
Major SSI (%)	3 (16.7)	0	2 (11.8)	0
Dehiscence (%)	2 (11.1)	6 (31.6)	3 (17.6)	5 (29.4)
Major dehiscence (%)	0	0	1 (5.9)	1 (5.9)
Lymphatic complications (%)	5 (27.8)	8 (42.1)	4 (23.5)	6 (35.3)
ACS (%)	0	3 (15.8)	1 (5.9)	1 (5.9)
LRTI (%)	0	1 (5.3)	1 (5.9)	0

ACS = acute coronary syndrome; LRTI = lower respiratory tract infection.

peripheral compartments, and capillary vasoconstriction can result from a drop as little as 0.2°C in skin temperature.[18] Hence, our temperature application may not have adequately enhanced skin perfusion intraoperatively, a time often considered to be influential for wound healing. The measurement of skin temperature surrounding the wound may have been more sensitive than core temperature in providing a better understanding of the physiological effect of active warming. To achieve this measurement, the OxyVu device could be used for simultaneous skin perfusion assessment. However, this would have been impractical, especially from the perspective of sterility during and after the operation.

This study was underpowered such that the target sample size of 76 patients was not achieved. Aiming to detect a 25% absolute increase in OHP by day 5 in these treatment arms might have been overly ambitious, perhaps the study should have focussed on one treatment arm, that is, using one adjunct alone or in combination. This would have provided a better powered study, with more patients in each arm to reduce the risk of type 2 error.

Despite the lack of benefit found for wound healing, the use of perioperative high-dose oxygen and warming to normothermia should still be advocated in vascular surgery due to their benefits in terms of anesthesia, coagulation, and reducing surgical site infections and cardiac events.[4,19,20]

Table 7 – Primary and secondary patency, limb salvage, and mortality rates in the four groups at 1 and 12 mo post IIB surgery.

Group	Control	Oxygen	Ilomedin	Temp
Primary patency rate (%)				
1 mo	89	84	94	88
12 mo	47	51	40	58
Secondary patency rate (%)				
1 mo	94	89	100	94
12 mo	58	61	53	81
Limb salvage (%)				
12 mo	72	95	82	94
Overall survival (%)				
12 mo	89	95	95	88

Conclusions

The three adjuncts examined in this study did not have beneficial effects on wound healing and tissue oxygenation at the surgical wound in the acute phase. Perfusion to the foot was enhanced by Ilomedin at day 5; however, the elevated deoxyhemoglobin level in the oxygen and temperature groups requires further investigation.

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

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