Evaluation of Predictive Values of an Automatic Device Measuring Oximetry in Free Flaps

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Summary: Free-flap monitoring is challenging to perform in some centers. It requires the availability of trained health care personnel for 24 hours a day and seven days a week. Many methods had been proposed for flap monitoring, and none of them are superior to clinical evaluation. This study aimed to present a murine model to evaluate the accuracy (sensitivity, specificity, and the positive or negative predictive values) of a device. Wistar rats weighing 240–490 g were included for intervention and data collection. A murine model of left inferior epigastric vessel flaps was implemented. Intermittent pedicle clamping was performed to calculate the accuracy of the device that detects flow obstruction. The general variables studied were age, weight, and gender. The sensitivity, specificity, and negative or predictive values were calculated. The results showed a sensitivity of 97%, a specificity of 95% with a positive predictive value of 95%, and negative predictive value of 97%. The sensitivity and specificity showed excellent results within the range of clinical security. We require more data to analyze the multiparameter monitoring to see if it is feasible and cost-effective. *(Plast Reconstr Surg Glob Open 2021;9:e3819; doi: 10.1097/GOX.0000000000003819; Published online 22 September 2021.)*

INTRODUCTION

In microsurgery, free-flap surveillance is not a new topic but is still under research. Free-flap loss is up to 5%–10% in most case series.[1] Previously, Creech,[2] Miller,[3] and Jones[4] provided some recommendations for the ideal flap monitoring device. Up to date, no device meets all these recommendations. To our knowledge, no device or method overcomes clinical evaluation with parameters such as color, turgidity, surface temperature, and capillary refill time. Several methods have been proposed for flap monitoring, such as acoustic doppler echography, color duplex ultrasonography, implantable doppler, flow coupler, laser doppler flowmetry, and near-infrared and white light spectroscopy, among others.[5] Nevertheless, none of them is superior to clinical evaluation as the most reliable monitoring technique.

Near-infrared spectroscopy (NIRS) uses an infrared light emitter and a sensor to measure blood flow and oxygen percentage in the tissue, which is determined by the amount of light absorbed.[3,6–11] Hemoglobins absorb these near-infrared lights in different wavelengths depending on whether they are deoxygenated (660 nm) or oxygenated (940 nm).[12] The literature has extensive revisions on many devices and applications for medicine. In microsurgery, the primary devices that use NIRS and oximetry are VIOptix ODISsey tissue oximeter (ViOptix Inc., Fremont, Calif.)[9] and INVOS (Medtronic, Dublin, Ireland).[13] Both had been widely explored in the literature. Most authors concluded that large-scale, randomized, multicentric clinical trials are necessary, and more data are needed to recommend these devices.[5,11] NIRS is a promising technology that could be accessible, low cost, and effective.

Previously we presented a device that measures the temperature of a free flap and that of the adjacent skin. Whenever the differential temperature between both was greater or lower than 35.6°F (2°C), a text message was sent to a mobile phone. This device provided a high specificity of 100% but, unfortunately, a low sensitivity of 7.99%.[14] In the future, we plan to combine the temperature and NIRS to create a multiparameter monitor. On this occasion, we worked

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with a NIRS sensor, GY-MAX30100 (Maxim Integrated, San Jose, Calif.),[15] to develop a device that monitors both temperature and oximetry. As an initial step, we need to evaluate the biological accuracy of the GY-MAX30100 to know if it is a suitable candidate for this combination. In this murine model, we did not measure temperature because anesthesia causes hypothermia in the subjects. To control it, we use thermal devices such as blankets and hot air heaters, which are direct bias to surface temperature. Consequently, in this model, only the oximetry was measured, and previously, hot water was used as a proof of concept to avoid bias.

To our knowledge, there is no multiparameter (oximetry and temperature) device available for microsurgeons. Therefore, sometimes it is difficult to conduct proper free-flap surveillance. Extensive literature revisions describe how challenging it could be to monitor free flaps in the first hours. This line of investigation aims to manufacture a multiparameter device that measures and combines multiple monitoring methods. Adding multiple parameters may bring the best of every method instead of hoping that only one could replace clinical evaluation.[16] We do not intend to replace clinical evaluation, but we want to bring additional remote-automatic surveillance to reduce free-flap monitoring burdens. This study aimed to present a murine model that will show the accuracy (sensitivity, specificity, positive predictive value, and the negative predictive value) of a device.

METHODS

Wistar rats weighing 240–490 g were included for flap elevation and for recording data. We calculated the sample based on data, risk, and benefits. The general variables studied were age, weight, and gender. All procedures performed in studies involving animal participants followed the ethical standards of the institutional and national research committee, and conformed to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All procedures were approved and performed in regulation with Official Mexican Standard NOM-062-ZOO-199 and International Council for Laboratory Animal Science.

We used the following institutional protocols: anesthetic, aseptic-antiseptic, antibiotic prophylaxis (enrofloxacin 5 mg/kg subcutaneously), and systemic response management with steroids (dexamethasone 0.1 mg/kg intraperitoneally). A single dose of pentobarbital (45 mg/kg) was administered intraperitoneally. Supplementary oxygen was administered via a nose cone, and vital signs were monitored throughout the procedure. Eye lubricant was applied routinely to prevent corneal lesions. A single local dose of lidocaine (1 mg/kg) was administered in the region of the incision.

Surgical Procedure

We used a standardized model to simulate a free-flap pedicle obstruction. We simulated pedicle flow interruption or thrombosis with a clamp. Since we performed the clamping, we took this event as the gold standard. The model was implemented following the technique described

Takeaways

Question: Free-flap monitoring is challenging and a burden in many microsurgery centers. The problem is that at any time in the first 72 hours pedicle thrombosis may occur and it could be treated before free-flap failure manifests. Up to date, no device is able to effectively monitor flap parameters, and clinical evaluation is still the gold standard for free-flap surveillance, making it challenging and a burden for health-care providers. So we want to create a multiparameter device that can continuously monitor multiple parameters of temperature and oximetry. The question is: What are the sensitivity, specificity, positive predictive values, and negative predictive values of this device?

Findings: We used an animal model of a pedicle flap and performed clamping to simulate pedicle thrombosis. The device took readings, and we controlled the clamping; so we can see how many events of clamping the device predicted as positive or negative. We found a sensitivity of 97%, a specificity of 95% with positive predictive value of 95%, and negative predictive value of 97%.

Meaning: This multiparameter device is accurate.

by Ballestin et al,[17] with a cutaneous flap based on the inferior epigastric vessels.

Sampling biases were controlled by shaving the abdominal area where the probe would be placed. After verifying an adequate anesthetic plane, a 3 × 6 cm skin flap was raised with a scalpel and sharp dissection. At all times, pedicles were protected to avoid manipulation. In this model, we did not dissect the pedicles adventitia to avoid spasm or perfusion bias.[17] However, we did skeletonize the pedicle to identify it and to ensure pedicle occlusion with the clamp. The flap was placed in a rigid nylon mesh with squares of 5 × 7 cm to avoid curling, and was secured to that mesh using nylon simple sutures. The light probe was facing directly through one of the mesh holes to avoid reflection sampling bias. Then with a microsurgery arterial clamp, the pedicle was clamped to simulate arterial and venous simultaneous occlusion. The surgical procedure and data sampling are summarized in Supplemental Digital Content 1. (**See figure, Supplemental Digital Content 1,** which displays how the flap is raised, and the pedicle is left intact. The bottom three images show clamping and unclamping procedures. **http://links.lww.com/PRSGO/B785**.) During the procedure, electric blankets were used to prevent hypothermia in the subjects.

Device Description and Data Sampling

The device is based on an Arduino-Nano V3 (Arduino, Somerville, Mass.)[18] with an ATmega328 (Atmel, San Jose, Calif.) microcontroller. It is wired to two LM35 (Texas Instruments, Dallas, Tex.) thermometers, the GY-MAX30100 (Maxim Integrated, San Jose, Calif.),[15] and a display as shown in Figure 1. The oximeter and one thermometer is attached to the flap, while a second thermometer is attached to the adjacent skin to measure the differential temperature, as described in our previous work.[14]
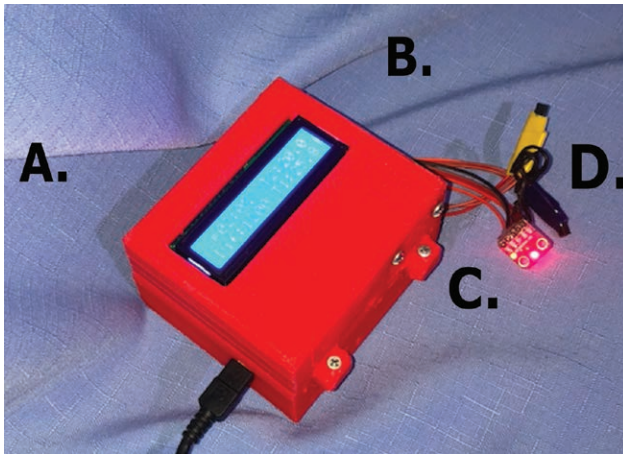
Fig. 1. Image of the device and its components. A, The main case with the microcontroller. B, The thermometer of adjacent skin. C, The oximeter GY-MAX30100. D, The thermometer for the free-flap surface.

The source code instructed the microcontroller to collect data every second, sampling two temperatures (the adjacent skin and flap skin) and the oximetry in the flap skin, to standardize sampling with no bias. We did not measure the temperature because the pharmacokinetics of general anesthesia has systemic repercussions, causing murine hypothermia; so it is mandatory to use artificial thermal heating to ensure the subject's security. In this model, we only measured the oximetry, and we previously performed an in vitro model to calculate the accuracy of the thermal sampling.[14]

Statistical Analysis

Data were organized in Excel (Microsoft, Redmond, Wash.) spreadsheets and then exported to RStudio (RStudio, Boston, Mass.) for statistical analysis. The sensitivity, specificity, negative predictive value, and positive predictive value were calculated.[17]

RESULTS

A total of three male subjects at 1 month of age and weighing 420, 490, and 350 g, respectively were included. One epigastric-based flap was raised in each subject in the left inguinal area, with no complications or eventualities. An estimated 307 samples were collected, and the summary of their screening data is listed in Table 1. Only a total of seven false-positive out of 170, and four false-negative

out of 137 samples were registered. The results showed a sensitivity of 97%, a specificity of 95% with positive predictive value of 95%, and negative predictive value of 97%.

DISCUSSION

There are devices available in some nations for free-flap surveillance. Microsurgery is increasing in developing countries. However, unfortunately, these devices are virtually impossible to acquire.[20] Therefore, manufacturing low-cost, accessible devices is imperative. Vioptix (ViOptix Inc., Fremont, Calif.) and Invos (Medtronic, Dublin, Ireland) perform formidably, and our device is not expected to compete against them. Still, a low-cost, reliable device is needed. Vioptix (ViOptix Inc., Fremont, Calif.) viability flat rates when used are exceptional and improved from 57.7% to 93.75%, whereas Invos (Medtronic, Dublin, Ireland)[21,22] reported a sensitivity of 100% and a specificity of 96%.[5] Further comparison between devices is out of the scope of this study, and a randomized clinical trial is mandatory. We will stay neutral for recommending one device over the other.

Limitations of Our Findings

We are aware that our findings have only internal validity. We do not recommend using the MAX30100 or our device in a clinical setting until the evidence is sufficient to recommend it. We still need to perform minor adjustments in software and hardware to ensure patient safety and to comply with local sanitary and legal regulations. We want to share our advancements in microsurgeons' feedback and inspire other developers to manufacture such a device.

We use only three subjects because, in this model, we had strict control of environmental variables. Furthermore, more importantly, we can reproduce the clamping event countless times, giving us multiple data without losing murine lives.

It is essential to state that we clamped artery and vein for internal validation purposes in this model simultaneously. In the future, we will present the oximetry changes with vein occlusion alone and artery occlusion alone in the function of time. However, first, we need evidence that the device performs perfectly.

We found seven false positives, and we believe that those were due to voltage variations in the circuit, and sampling speed. If we take many samples per minute, it is probable that the device could misread data. We are exploring the device wiring circuit, and we will use more spaced sampling to solve this problem.

The fabrication of the device is not finished, and more components could be needed. At this point, the overall cost of the device is around $500 US. It may be a more economic option, but we need more research and hardware improvements to make a valid economic analysis.

CONCLUSIONS

In this study, we presented the screening parameters for this new device in a controlled scenario, using a murine model. The sensitivity and specificity showed acceptable results and are within the range of clinical security. Nonetheless, we require more data to analyze

Table 1. Summary of Screening Data from the Device

	True (+)	True (−)	Total
Device (+)	163	7	170
Device (−)	4	133	137
Total	167	140	307
Outcome			
Sensitivity	97%		
Specificity	95%		
PPV	95%		
NPV	97%		

NPV, negative predictive value; PPV, positive predictive value.

the multiparameter monitoring to see if it is feasible and accessible. These findings show internal validity, and we do not recommend human trials at this moment.

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