Observational Study

Medicine® OPEN

Effective dose of dobutamine in augmenting free flap blood flow during reconstructive surgery of the lower extremity

Sung-Hoon Kim, MD, Young-Jin Moon, MD, Jae-Won Kim, MD, Jeong-Yeon Hong, MD, Wook-Jong Kim, MD*, Jai-Hyun Hwang, MD

Abstract

Success of surgical free flap transfer depends on achieving and maintaining adequate perfusion across the microvascular anastomosis. The purpose of this prospective study was to determine the optimal infusion rate of dobutamine to augment duplex ultrasound measured blood flow to the tissue flap during surgery.

Twenty-one patients undergoing general anesthesia for lower limb reconstructive surgery were recruited. The optimal dobutamine dose was evaluated using the modified Dixon's up-and-down method, starting at 6 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$, and then titrated in increments of 1 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$.

The optimal dose of dobutamine for improving blood flow to the tissue flap was 3.50 ± 0.57 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ in 50% of patients. The 95% effective dose of dobutamine calculated by probit analysis was 4.46 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ (95% confidence interval: 3.99–7.00 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$).

The results of our study suggest that a dobutamine infusion rate less than 5 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$provides significant improvement of blood flow to the tissue flap, while minimizing cardiovascular side effects.

Abbreviations: ED = effective dose, GA = general anesthesia.

Keywords: blood flow, dobutamine, free flap

1. Introduction

Reconstructive free flap surgery involves the transfer of free pedicle muscle flaps using a microsurgical technique. Success of surgical free flap transfer depends on achieving and maintaining adequate perfusion across the microvascular anastomosis.[1,2] Besides meticulous surgical technique, the mainstays for preventing vascular occlusion include the maintenance of normothermia, mild hypervolemia, and reduced blood viscosity. Maintaining of optimal blood flow through the vascular anastomoses is crucial for the success of such procedure. Thus, perioperative fluid and hemodynamic management by the anesthesiologist is crucial in preventing hypoperfusion of the transferred tissue and graft failure.[2]

The use of perioperative systemically administered vasoactive agent is generally avoided due to the fear that those vasoactive agents might hinder the blood flow and compromise the viability of the flap. However, several authors have been advocated that dobutamine, unlike other ionotropic, may increase free flap perfusion.[3–5] In a swine model, Corderio et al proposed that dobutamine increases both cardiac output and blood flow to island musculocutaneous flaps. They further stated that dopamine does not affect and that phenylephrine adversely affects flap blood flow.[3] Similarly, Suominen et al[4] documented that a dobutamine infusion of 8 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ resulted in increased flap blood flow as the result of higher cardiac output and decreased systemic vascular resistance; whereas a dopamine infusion of 8 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ had no effect on flap blood flow because of increase in systemic vascular resistance. In addition, Scholz et al[5] also demonstrated that blood flow to the flap significantly increased above baseline values with dobutamine infusion of 4 and 6 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$.

Despite the beneficial effect of dobutamine on flap perfusion, the optimal infusion rate for maximizing blood flow to the flap while minimizing the adverse effects is still unclear. Therefore, we undertook this study to evaluate the appropriate dose of dobutamine to improve free flap blood flow in patients undergoing low extremity reconstruction surgery under general anesthesia (GA).

2. Methods

Twenty-one patients were included in the study after institutional review board approval and written informed consent. The subjects were planned to undergo lower extremity reconstructive

Editor: Yan Li.

S-HK and Y-JM contributed equally to this work.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors have no conflicts of interest to disclose.

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

* Correspondence: Wook-Jong Kim, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea (e-mail: wookjong.kim@gmail.com).

Medicine (2019) 98:18(e15358)

Received: 23 August 2018 / Received in final form: 15 February 2019 / Accepted: 29 March 2019

http://dx.doi.org/10.1097/MD.0000000000015358

surgery using an anterolateral thigh free flap under GA. Patients were aged 21–59 years and were of ASA physical status I. Exclusion criteria included diabetes, hypertension, ischemic heart disease, cardiac arrhythmia, prior deep vein thrombosis, and peripheral vascular disease.

All subjects fasted at least 6 h before surgery, and no premedication was given. Upon arrival to the operating room, routine monitoring was initiated, comprising of non-invasive blood pressure, electrocardiography, and pulse oximetry. All patients were anesthetized by the same anesthesiologist and received intravenous fluid 10 mL·kg^{-1} Ringer's lactate solution prior to induction. GA was induced with standard doses of pentothal sodium, vecuronium, and fentanyl. The trachea was intubated, and mechanically controlled ventilation with 2–3 vol % sevoflurane in 50% oxygen-air was used to maintain the end-tidal carbon dioxide at 4.5–5.0 kPa. Throughout the entire study period, the core body temperature was continuously monitored in order to maintain normothermia with forced heating blankets. At the end of surgery, we checked the patients' hematocrit and tried to maintain between 30% and 35%, and packed red cells were given, if necessary.

Duplex sonography was taken at baseline (prior to the induction of anesthesia), before dobutamine infusion, and 15 min after dobutamine infusion. The investigator who monitored the patients' hemodynamics and flap blood flow parameters was blinded to the rate of dobutamine infusion. Duplex investigation was performed using an EUB 7500 HV (Hitachi Medical Corporation, Tokyo, Japan) with a high resolution (10 MHz) linear-array transducer. The probe position and 60° of angle were scrupulously maintained using a protractor and marks in every examination. Investigation of anastomosed donor arterial hemodynamics included time velocity integral, cross-sectional area, and volume flow. All data were measured three times during each examination by a single blinded investigator, and averaged values were used. The reproducibility of the duplex measurements had presented in our previous publication.[6]

The infusion of dobutamine was started before the flap anastomosis, and rate of dobutamine was determined by the response of the previously tested patient according to the Dixon's up-and-down method (using 1.0 μg·kg^{-1}·min^{-1} as a step size). The first patient received 6.0 μg·kg^{-1}·min^{-1} of dobutamine. To allow steady state conditions to be achieved, a pre-determined dose of dobutamine was continuously infused for 15 min. In the implementation of Dixon's up-down dose-finding method, augmentation of blood flow within ±5% of baseline was defined as a positive response. If the patient had a positive response, the dose of dobutamine was reduced for the successive subjects. On the contrary, a negative response was defined when the blood flow after 15 min of dobutamine infusion fell short of ±5% of baseline, which resulted in an increased dose for the next subject. To minimize the influence of surgical stimulation, all study-related measurements and procedures were performed during a natural break in the operation. If clinically significant hypertension (systolic blood pressure >180 mm Hg) or tachycardia (heart rate >120 bpm) occurred during the protocol, the patient was managed appropriately and excluded.

Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL). Data were collected from patients using Dixon's method to provide seven pairs of data where an increase in dobutamine dose changed a negative response to a positive response in successive patients. The dose of dobutamine with a 50% probability of sufficient improvement of blood flow was defined as the 50% effective dose (ED_{50}), and was determined by calculating the mean of the midpoint dose of the seven pairs of data described above. The ED_{50} and 95% effective dose (ED_{95}) were also determined using probit analysis. Repeated measures analysis of variance was used for the analysis of hemodynamic data, with *post hoc* testing by the Tukey method. A P value < .05 is considered a statistically significant difference.

Table 1

Patient characteristics and intraoperative variables, median [IQR] (range).

Parameters	
Sex; male/female	12/9
Age; year	46 [36.25–51.75] (21–59)
Weight; kg	65.8 [55.825–75.8] (40–87)
Height; cm	164.2 [159.375–171] (151.1–181)
Cause of surgery; n	
Traumatic injury	11
Malignant tumor of soft tissue	10
Operation time; min	319 [253–470] (203–708)
Anesthesia time; min	345 [299.5–497] (230–765)
Crystalloid solution; mL	1250 [900–2200] (550–2900)
Colloid solution; mL	500 [437.5–500] (300–1000)

3. Results

Twenty-one patients were enrolled in this study, of whom 12 were male and 9 were female. Patients' details are presented in Table 1.

Figure 1 plots the improvement of blood flow for each consecutive patient along with the Dixon's up-and-down sequence. The results of the calculations for the seven crossover pairs indicated that the ED_{50} of dobutamine for sufficient improvement of free flap blood flow during GA was 3.50 ± 0.57 μg·kg^{-1}·min^{-1}. Probit analysis showed that the ED_{50} and ED_{95} of dobutamine were 3.58 μg·kg^{-1}·min^{-1} (95% CI: 2.94–4.09 μg·kg^{-1}·min^{-1}) and 4.46 μg·kg^{-1}·min^{-1} (95% CI: 3.99–7.00 μg·kg^{-1}·min^{-1}), respectively (Fig. 2).

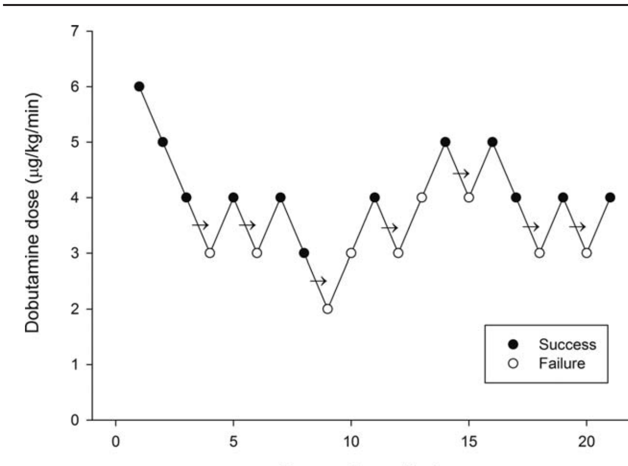

Figure 1. The response of 21 consecutive patients and the dose of dobutamine. The arrow indicates the midpoint dose for the cross-over to a positive response. The dose of dobutamine for improvement in free flap blood flow in 50% of patients was 3.50 ± 0.57 μg·kg^{-1}·min^{-1}.

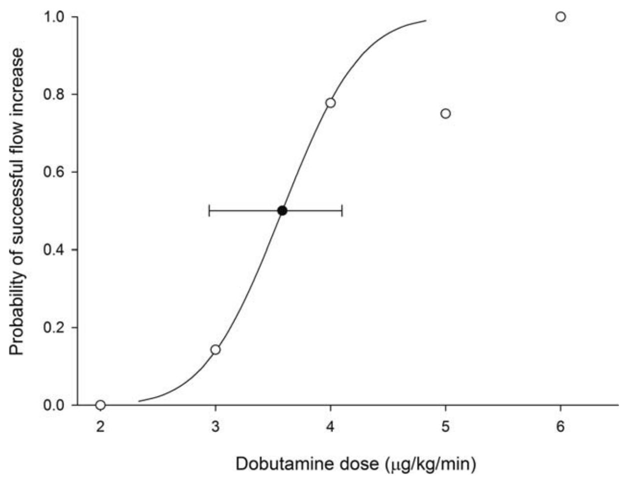

Figure 2. Dose–response curve from the probit analyses of individual dobutamine doses and the response to the infusion in the subjects. The doses of dobutamine at which there was a 50% and 95% probability of improving blood flow were 3.58 and 4.46 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively.

Patient hemodynamic data are shown in Table 2. Blood pressure prior to dobutamine infusion was significantly lower than at baseline ($P < .05$). After dobutamine infusion, SBP returned to baseline levels, whereas the diastolic pressure did not. After the completion of sonographic measurements and study protocol, one patient receiving 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and one patient receiving 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ experienced clinically significant hypertension. For these patients the infusion of dobutamine was ceased immediately.

4. Discussion

The results of our study demonstrated that the ED_{50} and ED_{95} of dobutamine for improvement of blood flow to the anastomosed free flap were 3.58 and 4.46 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. To our knowledge, this is the first report to determine the optimal dose of dobutamine for enhancing blood flow to the free flap during GA, and our results suggest that there is a significant augment of blood flow at relatively smaller doses of dobutamine compared with those previously suggested.

Anesthetic management for free flap surgery aims to optimize blood flow to the flap tissue across the anastomosis by increasing circulating blood flow and preventing peripheral vasoconstriction.[7,8] Although the effects of inhalational anesthetic agents on the regional blood flow in the free flap are not yet well known, most volatile anesthetics decrease blood pressure by decreasing total peripheral resistance and depressing myocardial contractility.[9] Importantly, it has been demonstrated that implementation of epidural anesthesia generated a significant enhancement of the arterial leg inflow contrasting the blood flow attenuation sustained with GA.[10–13] During prolonged operations under GA, patients may also become hypothermic and hypovolemic, which predisposes them to generalized vasoconstriction and diminished blood flow to the lower limb[14,15] and the transferred flap tissue.[8,9] Although overall blood flow in a free microvascular flap is complex, any cause of flow attenuation sustained with GA is believed to be harmful to the flap perfusion, such as profound hypotension, hypovolemia, anesthesia-induced decreases of myocardial contractility, and low cardiac output.[4,8]

Theoretically, dobutamine has advantages as a potent β_1- and β_2-agonist, which provides direct inotropic action coupled with systemic vasodilatation and afterload reduction. An adequate arterial blood pressure with vasodilatation ensures good tissue perfusion by providing sufficient regional blood flow, improving patency of the microvasculature, and maintaining the fluidity of the blood in the microcirculation.[7] In this respect, several authors have recently begun to advocate its use for improving flap blood flow, and in a swine model it was shown that flap blood flow is increased with dobutamine rates of 3, 6, and 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[3] In humans, there have also been a small number of reports that dobutamine may increase free flap perfusion[4,5]; however, the recommended doses of dobutamine are varied, ranging from 4 to 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In our study, the ED_{50} and ED_{95} of dobutamine for improving blood flow to the anastomosed flap above that of baseline were 3.58 and 4.46 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. These results imply that most patients could achieve sufficient enhancement of blood flow to the flap at dobutamine rates of even less than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. As the use of dobutamine is not fully harmless without side effects, a low-dose infusion of dobutamine would minimize potential adverse effects, while still rendering beneficial effects on flap perfusion.

Blood flow in free vascularized flap tissue is different from normal tissue in several respects. For instance, free vascularized tissue is subjected to complete denervation, and although the arteries in free flaps have no neurogenic response, they still respond to pharmacologic agents. Lorenzetti[16] demonstrated that blood flow through the free flap does not dependent on

Table 2

Changes of blood flow to free flap, cardiovascular and systemic variables, median [IQR] (range).

	Baseline	Pre-infusion	Post-infusion
FV; $mL \cdot min^{-1}$	9.36 [2.95–17.01] (1.04–21.28)	6.24 [3.253–14.78] (0.69–21.28)*	9.0 [4.86–19.71] (1.36–62.64)
CSA; cm^2	0.03 [0.02–0.0375] (0.01–0.07)	0.03 [0.02–0.04] (0.01–0.06)	0.03 [0.0225–0.0475] (0.01–0.05)
SBP; mm Hg	123 [112.75–145.25] (102–170)	97 [87.5–107.25] (81–147)*	131 [110–146.75] (96–155)†
DBP; mm Hg	84 [76.25–90] (62–117)	70 [63.75–76.5] (52–98)*	78 [75.25–81.5] (66–101)
MAP; mm Hg	73 [65.75–78.5] (43–107)	55 [50.5–60.75] (40–68)*	60 [53.5–62.75] (50–78)*
HR; $beat \cdot min^{-1}$	74 [70.25–92.5] (52–110)	71 [62.25–86.75] (51–112)	72 [59–96.5] (54–126)
Temperature; °C	37.1 [36.7–37.3] (35.8–37.7)	36.9 [36.3–37.2] (35.7–37.6)	37.0 [36.5–37.2] (35.8–37.7)
$EtCO_2$; kPa	4.7 [4.3–4.8] (4.1–5.4)	4.4[4.2–4.5] (3.7–4.9)	4.7 [4.1–4.9] (4.0–5.3)

CSA = cross-sectional area, DBP = diastolic blood pressure, $EtCO_2$ = end tidal carbon dioxide, FV = flow volume, HR = heart rate, MAP = mean arterial pressure, SBP = systolic blood pressure.
* $P < .05$ compared with baseline.
† $P < .05$ compared with pre-infusion.

recipient artery flow, and that the flow in the free flap rises to the level of donor artery flow after the completion of the anastomosis. Furthermore, Suominen et al[4] showed that 8 μg·kg^{-1}·min^{-1} of dobutamine infusion increases blood flow in both donor and recipient arteries simultaneously, and it is known that inodilators cause systemic vasodilation, which includes the vessels of the transplanted tissue.[2] These results support that measuring the blood flow to the flap tissue at the donor artery, as a surrogate measure of recipient artery flow, may be valid in evaluating the flap blood flow. In addition, air in the graft may cause erratic flow pattern and vessel spasm in the graft or native artery. Thus, low or zero mean flow value could be shown without pulsation. In our study the surgeons did not have any problems in applying the Doppler probe, and it was not difficult to interpret the achieved data.

There are several limitations to our study. First, we did not evaluate whether intraoperative infusion of dobutamine decrease postoperative flap failure rate. Most flap failures is known to occur during the first 3 days after surgery.[2] Virtually no experimental or clinical study has been carried out on the effects of intraoperative inotropic agents on outcomes of free flap procedures. Further studies are warranted, particularly as non-invasive monitoring techniques are now available that allow continuous monitoring of blood flow in transferred tissue after surgery. Second, although the Doppler ultrasound method is non-invasive, it has not gained much popularity with clinicians because flow measurements by this technique are dependent on vessel diameter, vessel shape, probe angle, and motion artifacts. Despite this limitation, Doppler ultrasound has been suggested as useful in monitoring arterial blood flow in skin flaps, and reliability of the technique might be improved when the probe is placed around the supplying vessels.[9] Lastly, we did not checked actual changes in cardiac output or systemic vascular resistance during dobutamine infusion. We hope to see that in the next study, which may give us more insights in what is happening.

In conclusion, the optimal infusion rate of dobutamine for improving blood flow to the free tissue flap in 95% of patients undergoing lower limb reconstructive surgery is 4.46 μg·kg^{-1}·min^{-1}. The results obtained here suggest that if Doppler ultrasound or surrogate parameters for titration are unavailable during free flap surgery, <5 μg·kg^{-1}·min^{-1} of dobutamine would provide a significant improvement of blood flow to the free transferred flap, while minimizing cardiovascular side effects.

Acknowledgments

Thank you to the following: Dr. Ashish Bangaari (MIOT Hospitals, Chennai, Tami Nadu, India) for his linguistic revision of this manuscript.

Author contributions

Conceptualization: Sung-Hoon Kim, Jae-Won Kim, Jeong-Yeon Hong, Wook-Jong Kim, Jai-Hyun Hwang.
Data curation: Sung-Hoon Kim, Young-Jin Moon, Jae-Won Kim, Jeong-Yeon Hong, Wook-Jong Kim.
Formal analysis: Sung-Hoon Kim.
Investigation: Wook-Jong Kim.
Methodology: Young-Jin Moon.
Supervision: Sung-Hoon Kim, Jai-Hyun Hwang.
Validation: Sung-Hoon Kim, Young-Jin Moon, Wook-Jong Kim.
Writing – original draft: Sung-Hoon Kim, Wook-Jong Kim.
Writing – review & editing: Sung-Hoon Kim, Young-Jin Moon, Jeong-Yeon Hong, Wook-Jong Kim.
Wook-Jong Kim orcid: 0000-0001-9178-3044.

References

[1] Harrison DH, Girling M, Mott G. Experience in monitoring the circulation in free-flap transfers. Plast Reconstr Surg 1981;68:543–55.
[2] Gardiner MD, Nanchahal J. Strategies to ensure success of microvascular free tissue transfer. J Plast Reconstr Aesthet Surg 2010;63:e665–73.
[3] Cordeiro PG, Santamaria E, Hu QY, et al. Effects of vasoactive medications on the blood flow of island musculocutaneous flaps in swine. Ann Plast Surg 1997;39:524–31.
[4] Suominen S, Svartling N, Silvasti M, et al. The effect of intravenous dopamine and dobutamine on blood circulation during a microvascular TRAM flap operation. Ann Plast Surg 2004;53:425–31.
[5] Scholz A, Pugh S, Fardy M, et al. The effect of dobutamine on blood flow of free tissue transfer flaps during head and neck reconstructive surgery. Anaesthesia 2009;64:1089–93.
[6] Hong JY, Ahn S, Kil HK. Changes of dorsalis pedis artery flow pattern after caudal block in children: observational study using a duplex sonography. Paediatr Anaesth 2011;21:116–20.
[7] Macdonald DJ. Anaesthesia for microvascular surgery: a physiological approach. Br J Anaesth 1985;57:904–12.
[8] Hagau N, Longrois D. Anesthesia for free vascularized tissue transfer. Microsurgery 2009;29:161–7.
[9] Sigurdsson GH, Thomson D. Anaesthesia and microvascular surgery: clinical practice and research. Eur J Anaesthesiol 1995;12:101–22.
[10] Haljamae H, Frid I, Holm J, et al. Epidural vs general anaesthesia and leg blood flow in patients with occlusive atherosclerotic disease. Eur J Vasc Surg 1988;2:395–400.
[11] Poikolainen E, Hendolin H. Effects of lumbar epidural analgesia and general anaesthesia on flow velocity in the femoral vein and postoperative deep vein thrombosis. Acta Chir Scand 1983;149:361–4.
[12] Hickey NC, Wilkes MP, Howes D, et al. The effect of epidural anaesthesia on peripheral resistance and graft flow following femorodistal reconstruction. Eur J Vasc Endovasc Surg 1995;9:93–6.
[13] Haljamae H. Effects of anesthesia on leg blood flow in vascular surgical patients. Acta Chir Scand Suppl 1989;550:81–7.
[14] Pflug AE, Foster C, Martin RW, et al. Limb blood flow. The influence of temperature during halothane-nitrous oxide anesthesia. Arch Surg 1980;115:616–21.
[15] Brismar B, Cronestrand R, Jorfeldt L, et al. Leg blood flow and central circulation at various blood volumes: a peroperative study of nine patients with varicose veins. Clin Sci Mol Med 1977;53:349–54.
[16] Lorenzetti F, Suominen S, Tukiainen E, et al. Evaluation of blood flow in free microvascular flaps. J Reconstr Microsurg 2001;17:163–7.