OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Cosmetic

Enhanced Recovery after Abdominoplasty Using Perisurgical Nutritional Supplementation

Leonard Harris, MD, MSc, FRCSC*
Peter Darby, MD, PhD, MSc, FRCPC†

Background: Nutritional supplements are common in other surgical specialties but not widely used in the plastic surgery setting. This study compares the surgical outcomes of patients using our standard ERAS protocol involving arnica and bromelain with an updated ERAS protocol using perisurgical nutritional supplementation using a staged administration of nutraceuticals.

Methods: In total, 300 female abdominoplasty patients were randomly provided with perioperative supplementation consisting of arnica and bromelain, or a 3-stage nutraceutical regimen containing arginine, citrulline, glutamine, bromelain, and vitamin C. Narcotic use in recovery and post-operative drainage were measured, and both groups completed a self-assessment of bruising coloration, days to independent activity, perceived pain, and documented the quantity of narcotic and non-prescription pain killers they took over a 14-day recovery period.

Results: There were 130 patients in the nutraceutical group and 80 in the arnica and bromelain group; patients were excluded due to non-compliance or due to incomplete data. Patients taking the nutraceutical regimen reported a shorter duration of pain and had a 41% reduction in narcotic use in recovery and experienced 48% less post-operative drainage. Home use of narcotic pain killers decreased by 25%. There also was a trend toward decreased and earlier clearing/maturation of bruising as well as return to daily activates without assistance. Patients also reported an increase in satisfaction with their surgical experience.

Conclusions: This study demonstrated that perioperative supplementation with nitric oxide precursors, antioxidants, and proteolytic enzymes in a staged fashion can positively affect post-operative outcomes and is an adjunct to enhanced surgical recovery protocols. *(Plast Reconstr Surg Glob Open 2020;8:e3314; doi: 10.1097/GOX.0000000000003314; Published online 22 December 2020.)*

INTRODUCTION

Enhanced recovery after surgery (ERAS) has been a standard of care in other surgical disciplines and is becoming more prevalent in plastic surgery.[1–4] The protocols focus on perioperative patient education, perioperative anti-inflammatories, antinausea medications, and non-narcotic pain control, including nerve blocks. The effects of perisurgical nutritional supplementation with different amino acids are well documented; however, there is scant literature investigating their role as part of an ERAS protocol. ERAS mainly focuses on multimodal pain control in an attempt to reduce narcotic usage. Targeting specific mediators during wound healing may yield better results. Most models of wound healing agree that healing occurs in phases, with the different cell types performing different functions.[5] These are generally divided into an inflammatory response, followed by a proliferative phase, and finally a regenerative phase (Fig. 1). This appears to be a generic biological response, as clean surgical wounds produce a biological profile similar to that of open traumatic wounds.

Nitric oxide is a critical mediator of wound healing and is upregulated during the inflammatory phase.[6] It has been shown to be of critical importance as a vasodilator, and as a regulator of vascular permeability, angiogenesis, tissue perfusion, immune defense, and collagen synthesis.[6–10] Arginine is the biological precursor to nitric oxide.[11] Studies have shown that surgical trauma as well as periods

*From the *Department of Surgery, Joseph Brant Hospital, Burlington, Ontario, Canada; and †Department of Anesthesia, McMaster Children's Hospital – Hamilton Health Sciences, Hamilton, Ontario, Canada.*

Received for publication April 24, 2020; accepted October 24, 2020.

Originally presented at the British Virgin Islands Plastic Surgery Workshop, January 2019.

DOI: 10.1097/GOX.0000000000003314

Disclosure: *The authors have no financial interest in any of the products used, nor commercial association.*

of intense stress can impair arginine production, making it a conditionally essential amino acid.[12–15] However, oral supplementation of arginine alone fails to increase blood arginine levels due to the first by-pass effect, and must be taken in conjunction with its precursor: citrulline.[16] Citrulline can be produced by the body from the precursor glutamine, through the "glutamine-citrulline-arginine pathway."[12] Glutamine is converted in the intestine to citrulline, which is then converted in the kidney to arginine. Perisurgical arginine and glutamine supplementation has been shown to produce significant positive effects on morbidity, wound healing, length of hospital stay, and mortality, and these aminoacids have been described as immunonutritional agents.[4,12,17–27] Existing perisurgical nutritional products focus on this pathway, with little effect on nitric oxide.[28]

Other supplements (such as bromelain—a proteolytic enzyme) have been used perioperatively to reduce hemolytic and necrotic byproducts, as well as to reduce inflammation and pain.[29,30] Perioperative oral supplementation has been shown to reduce ecchymosis and edema after rhinoplasty[31] and episiotomy.[29] Bromelain has also been shown to reduce pain and inflammation in oral surgery comparably to diclofenac sodium.[32] Arnica is a homeopathic remedy that is popularly recommended to patients for the reduction in bruising; however, recent reviews have shown that these claims are questionable.[33]

The aim of this study was to determine whether a staged supplementation of nitric oxide precursors, proteolytic enzymes, and antioxidants would have a synergistic effect on influencing recovery after cosmetic surgery—specifically abdominoplasty—compared with bromelain and arnica alone.

The endpoints measured were pain, as determined by narcotic use in recovery and upon discharge, as well as a self-reported pain scale (Fig. 2), amount of exudate drainage post operatively, time to independent activity, and visual clearing of bruising.

METHODS AND MATERIALS

After obtaining informed written consent from patients, they were alternately placed into 1 of the 2 groups, based on bookings of their surgeries. Only the booking clerk was privy to this grouping. All principles outlined in the Declaration of Helsinki were followed.

Patients received either a combination of arnica (30X) and bromelain (500 mg, 1500 GDU/g) perioperatively or a 3-stage nutraceutical regimen containing varying amounts of arginine, citrulline, glutamine, bromelain, and vitamin C. The dosing schedule was 3 days preoperatively, and 6 days postoperatively. Both products were provided in plain packaging, along with their dosing instructions.

All patients underwent an abdominoplasty procedure under general anesthesia with overnight post-operative

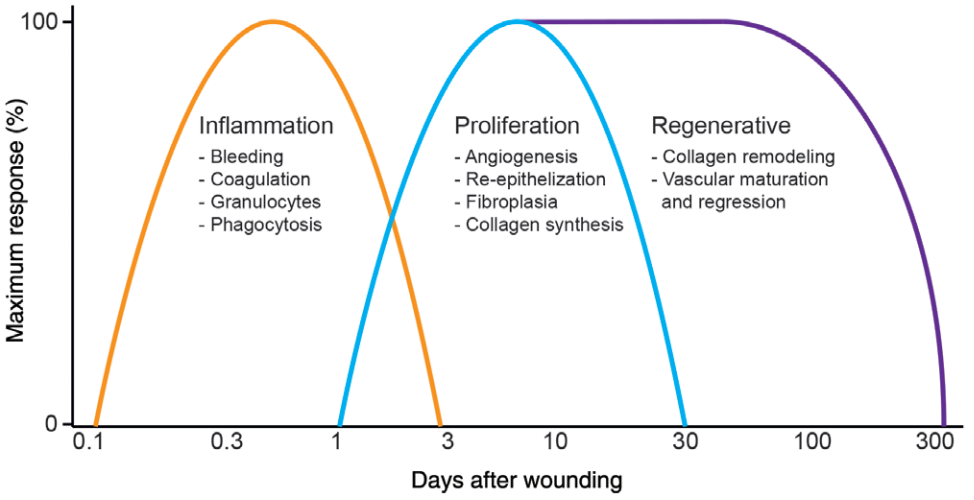

Fig. 1. Phases of wound healing.

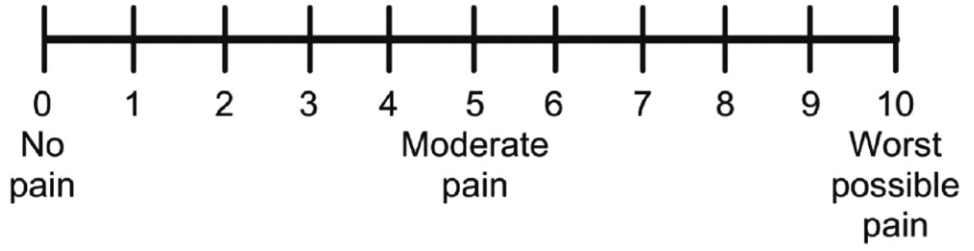

Fig. 2. Self-assessment pain scale.

recovery. Our standard ERAS protocol consists of pre and post-operative patient education, nursing care flowsheets, and regular contact with the patient after discharge. All patients received multimodal pain control consisting of acetaminophen 500 mg po, celocoxib 200 mg po, and ondansetron 16 mg po before induction, and intraoperative transverse abdominis plane and epigastric blocks using 0.25% bupivacaine. Drains were removed before discharge home the following day.

To minimize any placebo effect, the only difference between the 2 groups was the substitution of our regular supplementation using arnica and bromelain, with the neutraceutical regimen. The neutraceutical regimen used (Vivanta, Allexon Health Sciences Inc.) is a Health-Canada–approved natural health product that comprises a 3-stage regimen of varying ratios of arginine, citrulline, glutamine, bromelain, and vitamin C (Table 1).

Data on narcotic use and drainage were obtained from the patient's chart and monitored until discharge the next morning. Upon discharge, patients completed a daily self-assessment of pain, documented narcotic and non-prescription medication use and visual bruising coloration, and recorded their daily activities. Follow-up visits were at 1 week, 2 weeks, 1 month, and 3 months postoperatively.

STATISTICAL ANALYSIS

All data were compiled into Microsoft Excel. The data were organized by patient. Narcotic medications were coded separately, and subsequently converted to milligram morphine equivalents to standardize narcotic use across patients. Student's *t*-test was used to compare differences between means using IBM SPSS Statistics for Macintosh, version 25.

RESULTS

A total of 300 female abdominoplasty patients were enrolled in this study and operated upon by a single surgeon (Table 2). None of the patients were current smokers and none were diabetic. Of the 300 patients initially enrolled, only data from 210 were included. Exclusion of data was due to non-compliance with taking the supplements post operatively, or failing to complete the daily self-assessment. Narcotic use was calculated from the chart administration record and normalized to 1-mg morphine equivalents. Drainage was measured by the nurses and recorded on the patient chart.

In the post-operative recovery period, patients supplemented with the staged nutraceutical program required 41% less narcotic that those supplemented with arnica and bromelain. This trend continued upon discharge, with this cohort of patients using 25% less acetaminophen with codeine than their counterparts (Table 3). The staged nutraceutical group also reported a faster reduction in pain scores when compared with the group receiving arnica and bromelain (Fig. 3).

There was a significant reduction of post-surgical drainage in patients receiving the nutraceuticals (Table 3). These patients also reported being able to function independently approximately 2 days earlier than the group receiving arnica and bromelain.

Table 1. Composition of Nutritional Supplementation

	Step 1 : Day 1–3	Step 2: Day 4–6	Step 3: Day 7–9
Vitamin C	500 mg	500 mg	500 mg
Bromelain 150 GDU/g	500 mg	750 mg	0 mg
Glutamine	2000 mg	2500 mg	0 mg
Arginine HCL	500 mg	0 mg	2000 mg
Citrulline maleate 2:1	500 mg	500 mg	2000 mg

Table 2. Patient Demographics

	Vivanta	Arnica/Bromelain
No. patients	130	80
Age (mean)	47.3 ± 8.77	45.8 ±1 0.22
BMI, kg/m^2	26.33 ± 4.71	25.63 ± 4.13
Gender	130 women: 0 men	80 women: 0 men

DISCUSSION

The importance of nutritional supplementation, in particular with arginine and glutamine, has received significant attention because of the positive effects on wound healing, morbidity, mortality, and length of hospital stay when given perioperatively.[4,12,17–27] The mechanistic action of arginine, citrulline, and glutamine centers around their roles in nitric oxide production and the role nitric oxide mediation of various metabolic pathways.[6–10] Nitric oxide mediates host immune defense[6,7,34] while also exhibiting protective effects on the cardiovascular system by acting as a vasodilator.[35] Nitric oxide is also a potent mediator of vascular permeability both by acting directly on vascular endothelium, and by modulation of blood flow.[36] The role of nitric oxide is of great importance in wound healing,[6] but the natural glutamine-citrulline-arginine pathway can be impaired after surgical trauma.[35] Pre-surgical fasting also results in a drop in glutamine, arginine, and citrulline levels as well as the production of a number of inflammatory mediators.[14,15] The combination of these 2 factors requires an exogenous source of arginine to correct,[13,17,37] as deficiencies can lead to immunosuppression, impaired recovery, and altered vascular function.[7,10] Nutritional supplementation can influence the inflammatory phase of wound healing by its direct effects on nitric oxide levels.

The regenerative phase of wound healing is characterized by the removal of inflammatory products, angiogenesis, and collagen synthesis.[5,8] Tissue ischemia, induced by surgical trauma, causes an anaerobic cellular metabolism, leading to acidosis, as well as decreased cellular glycogen and ATP levels, which cause reduced cell membrane function, vascular endothelial adhesions, and an upregulation of clotting pathways.[6,37] After the restoration of blood flow by angiogenesis, free radicals cause further damage to the ischemic tissue by neutrophil influx and depletion of nitric oxide, aggravating interstitial edema, vasoconstriction, the accumulation of toxins, and the production of pro-inflammatory mediators.[38,39] This ischemia-reperfusion process diminishes cell function and impairs wound

Table 3. Results of Measured Outcomes

Outcomes (mean ± SD)	Vivanta	Arnica/Bromelain	Change %
Recovery narcotic use (morphine equivalents)	3.8 ± 0.6	7.8±1.6	41%*
Post-operative drainage (mL)	144 ± 23	277 ± 37	48%†
Home oral narcotic use (no. pills)	12.9 ± 6.8	17.2 ± 4.3	25%*
Days to independent activity	3.5 ± 1.32	5.7 ± 0.58	37%†

*$P < 0.001$.
†$P < 0.01$.

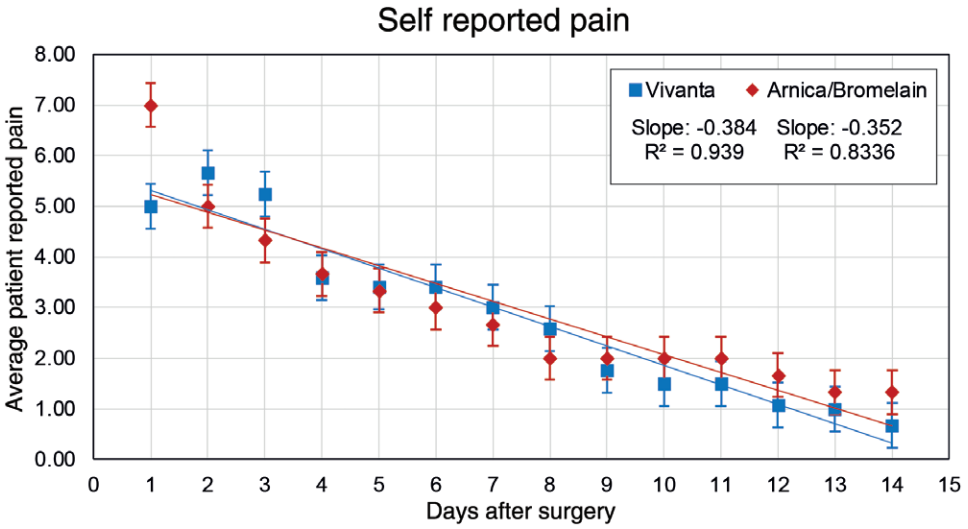

Fig. 3. Rate of decrease in patient reported pain (Mean ± SEM). Rate of change is approximately 10% faster for Vivanta.

healing. Nitric oxide and glutamine supplementation has been shown to protect against both ischemia-reperfusion injury and to further modulate collagen synthesis.[6,8,36,39]

This study examined the role of staged nutritional supplementation on post-surgical recovery. While most studies concentrated on the immune modulating role of arginine and glutamine supplementation, this study is the first to show a significant reduction of pain and narcotic requirements.

Reduction in Narcotic Use

Supplementation with the staged nutraceutical regimen reduced narcotic use both in the post-surgical recovery room and after the patient was discharged home (Table 3). A reduction of 41% in morphine equivalents in recovery was observed and a 25% reduction in use of oral analgesics containing narcotics upon the 2 weeks of home recovery. Self-assessed pain of patients who took the nutraceutical also decreased on average 10% faster than that reported in the arnica/bromelain group (Fig. 3). Most patients in the nutraceutical group who stopped taking oral analgesics containing narcotics after 3 days reported that pain severity as well as the duration was decreased. Patients also reported a faster return to independent activity. This reduction in pain was unexpected because the nutraceutical compounds have no reported analgesic properties. We would hypothesize that the supplementation with perioperative nutraceuticals led to a blunting of the inflammatory response to tissue injury, resulting in less edema/exudate, and less pain postoperatively. This observation may also be due to an effect of the antioxidant supplementation.

Reduction in Bruising

Patients also reported faster clearing of bruising. The role of proteolytic enzyme supplementation is still not certain, as the design and reporting mechanism of this study makes interpretation of the data highly subjective.

Future Work

Because the control group also took the proteolytic enzyme bromelain, these results may suggest that an increase in nitric oxide and the subsequent antioxidant and vasodilation effects may work synergistically to improve the outcomes measured. The mechanism of action of proteolytic enzyme supplementation has not been well studied and further research focusing on inflammatory biomarkers and vascular permeability is required to confirm this hypothesis.

CONCLUSIONS

This study demonstrated that perioperative supplementation with nitric oxide precursors, antioxidants, and proteolytic enzymes in a staged fashion can positively affect post-operative outcomes. This supplementation reduced recovery narcotic use by 41%, post-operative drainage by 48%, and home oral analgesic containing narcotic use by

25%. This in turn reduced the time it took for the patient to return to regular activities. More research is needed to support the mechanism behind this marked reduction in pain.

Leonard Harris, MD, MSc, FRCSC
Department of Surgery
Joseph Brant Hospital
3532 Commerce Court
Burlington, ON
Canada L7N 3L7
E-mail: harris@drharris.on.ca

REFERENCES

1. Temple-Oberle C, Shea-Budgell MA, Tan M, et al; ERAS Society. Consensus review of optimal perioperative care in breast reconstruction: Enhanced Recovery After Surgery (ERAS) Society recommendations. *Plast Reconstr Surg.* 2017;139:1056e–1071e.
2. Astanehe A, Temple-Oberle C, Nielsen M, et al. An enhanced recovery after surgery pathway for microvascular breast reconstruction is safe and effective. *Plast Reconstr Surg Glob Open.* 2018;6:e1634.
3. Bartlett EL, Zavlin D, Friedman JD, et al. Enhanced recovery after surgery: the plastic surgery paradigm shift. *Aesthetic Surg J.* 2018;38:676–685.
4. Weimann A, Braga M, Harsanyi L, et al; DGEM (German Society for Nutritional Medicine); ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN guidelines on enteral nutrition: surgery including organ transplantation. *Clin Nutr.* 2006;25:224–244.
5. Martin P, Nunan R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. *Br J Dermatol.* 2015;173:370–378.
6. Witte MB, Barbul A. Role of nitric oxide in wound repair. *Am J Surg.* 2002;183:406–412.
7. Nieves C Jr, Langkamp-Henken B. Arginine and immunity: a unique perspective. *Biomed Pharmacother.* 2002;56:471–482.
8. Schäffer MR, Tantry U, Gross SS, et al. Nitric oxide regulates wound healing. *J Surg Res.* 1996;63:237–240.
9. Shi HP, Most D, Efron DT, et al. Supplemental L-arginine enhances wound healing in diabetic rats. *Wound Repair Regen.* 2003;11:198–203.
10. Wu G, Bazer FW, Davis TA, et al. Arginine metabolism and nutrition in growth, health and disease. *Amino Acids.* 2009; 37:153–168.
11. Morris SM Jr. Arginine: beyond protein. *Am J Clin Nutr.* 2006;83:508S–512S.
12. Brinkmann SJ, Buijs N, Vermeulen MA, et al. Perioperative glutamine supplementation restores disturbed renal arginine synthesis after open aortic surgery: a randomized controlled clinical trial. *Am J Physiol Renal Physiol.* 2016;311:F567–F575.
13. Morris SM. Arginine metabolism: boundaries of our knowledge. *J Nutr.* 2007;137:1602S–1609S.
14. Vissers YL, Dejong CH, Luiking YC, et al. Plasma arginine concentrations are reduced in cancer patients: evidence for arginine deficiency? *Am J Clin Nutr.* 2005;81:1142–1146.
15. Barbul A, Fishel RS, Shimazu S, et al. Intravenous hyperalimentation with high arginine levels improves wound healing and immune function. *J Surg Res.* 1985;38:328–334.
16. Suzuki T, Morita M, Hayashi T, et al. The effects on plasma L-arginine levels of combined oral L-citrulline and L-arginine supplementation in healthy males. *Biosci Biotechnol Biochem.* 2017;81:372–375.
17. Brinkmann SJH, Buijs N, Luttikhold J, et al. Preoperative oral nutritional interventions in surgery, including arginine- and glutamine-enhanced supplements. *CAB Rev Perspect Agric Vet Sci Nutr Nat Resour.* 2013;8:1–4.
18. Yue C, Tian W, Wang W, et al. The impact of perioperative glutamine-supplemented parenteral nutrition on outcomes of patients undergoing abdominal surgery: a meta-analysis of randomized clinical trials. *Am Surg.* 2013;79:506–513.
19. Debats IBJG, Wolfs TGAM, Gotoh T, et al. Role of arginine in superficial wound healing in man. *Nitric Oxide* 2009;21:175–183.
20. Marik PE, Flemmer M. Immunonutrition in the surgical patient. *Minerva Anestesiol.* 2012;78:336–342.
21. Wachtler P, Axel Hilger R, König W, et al. Influence of a preoperative enteral supplement on functional activities of peripheral leukocytes from patients with major surgery. *Clin Nutr.* 1995;14:275–282.
22. Houdijk AP, Rijnsburger ER, Jansen J, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet.* 1998;352:772–776.
23. Wischmeyer PE, Dhaliwal R, McCall M, et al. Parenteral glutamine supplementation in critical illness: a systematic review. *Crit Care.* 2014;18:R76.
24. Avenell A. Symposium 4: Hot topics in parenteral nutrition Current evidence and ongoing trials on the use of glutamine in critically-ill patients and patients undergoing surgery. *Proc Nutr Soc.* 2009;68:261–268.
25. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks M. A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. *Clin Nutr.* 2013;32:213–223.
26. Sacks GS, Genton L, Kudsk KA. Controversy of immunonutrition for surgical critical-illness patients. *Curr Opin Crit Care.* 2003;9:300–305.
27. Senkal M, Zumtobel V, Bauer KH, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch Surg.* 1999;134:1309–1316.
28. Williams JZ, Abumrad N, Barbul A. Effect of a specialized amino acid mixture on human collagen deposition. *Ann Surg.* 2002;236:369–375.
29. Golezar S. Ananas comosus effect on perineal pain and wound healing after episiotomy: a randomized double-blind placebo-controlled clinical trial. *Iran Red Crescent Med J.* 2016; 18:e21019.
30. de AC Almeida R, de Sousa Lima FCM, do E Vasconcelos BC. Is bromelain an effective drug for the control of pain and inflammation associated with impacted third molar surgery? Systematic review and meta-analysis. *Int J Oral Maxillofac Surg.* 2019;48:651–658.
31. Seltzer AP. Minimizing post-operative edema and ecchymoses by the use of an oral enzyme preparation (bromelain). A controlled study of 53 rhinoplasty cases. *Eye Ear Nose Throat Mon.* 1962;41:813–817.
32. Majid OW, Al-Mashhadani BA. Perioperative bromelain reduces pain and swelling and improves quality of life measures after mandibular third molar surgery: a randomized, double-blind, placebo-controlled clinical trial. *J Oral Maxillofac Surg.* 2014;72:1043–1048.
33. Brito N, Knipschild P, Doreste-Alonso J. Systematic review on the efficacy of topical arnica montana for the treatment of pain, swelling and bruises. *J Musculoskelet Pain.* 2014;22:216–223.
34. Iuvone T, Van Osselaer N, D'Acquisto F, et al. Differential effect of L-NAME and S-methyl-isothiourea on leukocyte emigration in carrageenin-soaked sponge implants in rat. *Br J Pharmacol.* 1997;121:1637–1644.
35. Barbul A, Lazarou SA, Efron DT, et al. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery.* 1990;108:331–337.

36. Sessa WC. Molecular control of blood flow and angiogenesis: role of nitric oxide. *J Thromb Haemost.* 2009;7(suppl 1):35–37.
37. Aivatidi C, Vourliotakis G, Georgopoulos S, et al. Oxidative stress during abdominal aortic aneurysm repair–biomarkers and antioxidant's protective effect: a review. *Eur Rev Med Pharmacol Sci.* 2011;15:245–252.
38. Marre D, Hontanilla B. Increments in ischaemia time induces microvascular complications in the DIEP flap for breast reconstruction. *J Plast Reconstr Aesthet Surg.* 2013;66:80–86.
39. Zhang WX, Zhou LF, Zhang L, et al. Protective effects of glutamine preconditioning on ischemia-reperfusion injury in rats. *Hepatobiliary Pancreat Dis Int.* 2011;10:78–82.