Effects of Perisurgical Nutritional Supplementation on Outcomes After Abdominoplasty

Leonard Harris* MD, MSc, FRCSC and Peter Darby MD, PhD, MSc, FRCPC
*E-mail: harris@drharris.on.ca

From the Department of Surgery, Joseph Brant Hospital, Burlington, Ontario and the Department of Anesthesia, Hamilton Health Sciences, Hamilton, Ontario.

Updated: 11/27/2018. This article has been submitted for review. Changes may be made before publication.

ABSTRACT: 210 female abdominoplasty patients were randomly provided with perioperative supplementation consisting of arnica and bromelain, or Vivanta (a three-stage nutraceutical regimen). 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. There were 130 patients in the Vivanta group and 80 in the arnica and bromelain group. The patients taking Vivanta reported a significantly 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 to decreased and earlier clearing/maturation of bruising as well as return to daily activates without assistance. Patients also reported an increase in satisfaction with the surgical experience overall.

Introduction

Most models of wound healing agree that it occurs in phases, with the appearance of different cell types performing different functions [1]. These are generally divided into an inflammatory response, followed by a proliferative phase, and finally a regenerative phase [1] (*Figure 1*). This appears to be a generic biological response as clean surgical wounds produce a similar biological profile as open traumatic wounds.

Nitric oxide (NO) is a critical mediator of wound healing and is upregulated during the inflammatory phase [2]. It has been shown to be of critical importance as a vasodilator, regulator of vascular permeability, angiogenesis, tissue perfusion, immune defense and collagen synthesis [2-7]. Arginine is the biological precursor to nitric oxide [8]. Studies have shown that surgical trauma as well as periods of intense stress can impair arginine production, making it a conditionally essential amino acid [10-13]. 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 [8]. Citrulline can be produced by the body from the precursor glutamine, through the 'glutamine-citrulline-arginine pathway' [10]. Glutamine is converted in the intestine to citrulline, which is then converted in the kidney to arginine. Perisurgical arginine and glutamine supplementation have been shown to have significant positive effects on morbidity, wound healing, hospital length of stay and mortality and have been described as immunonutritional agents [10,14-25]. Existing perisurgical nutritional products focus on this pathway with little effect on nitric oxide [9].

Other supplements such as bromelain, a proteolytic enzyme, have been used perioperatively to reduce hemolytic and necrotic byproducts, as well as reduce inflammation and pain [26]. Perioperative oral supplementation has been shown to reduce ecchymosis and edema after rhinoplasty [27] and episiotomy [26]. Bromelain has also been shown to reduce pain and inflammation in oral surgery comparably to diclofenac sodium [28].

Arnica is a homeopathic remedy which is popularly recommended to patients for the reduction in bruising, however recent reviews have shown that these claims are questionable [29].

The aim of this study was to determine if 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 to bromelain and arnica alone.

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

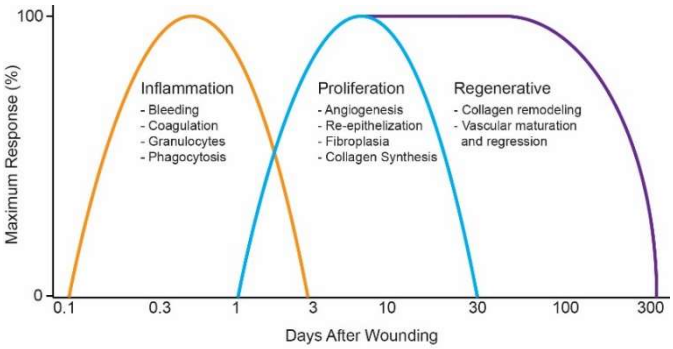

Figure 1: Phases of wound healing.

Methods and Materials

Patients were randomized into two groups (detailed in *Table* 1) receiving either the nutritional supplement Vivanta (Allexon Health Sciences Inc.); a three-stage regimen of varying ratios of: arginine, citrulline, glutamine, bromelain and vitamin C; or a combination of arnica (30X) and bromelain (500mg, 1500GDU/g) perioperatively. The dosing schedule was 3 days preoperatively, and 6 days postoperatively.

All patients underwent an abdominoplasty procedure under general anesthesia with overnight post-operative recovery. All patients received multimodal pain control consisting of acetaminophen 500mg po, celocoxib 200mg po, and ondansetron 16mg po preoperatively, and intraoperative transverse abdominus plane and epigastric blocks using 0.25% bupivacaine. Drains were removed upon discharge home the following day. Narcotic use and drainage was monitored until discharge and patients completed a self-

assessment of pain, documented narcotic and non-prescription medication use, visual bruising coloration and recorded their daily activities. Follow up visits were at one week, two weeks and one month three months postoperatively.

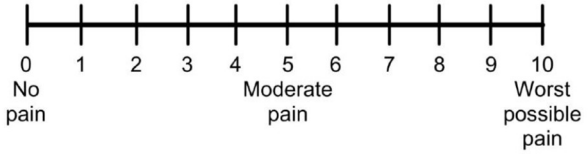

Figure 2: Self-assessment pain scale.

Results

A total of 210 female abdominoplasty patients were enrolled in this study and operated upon by a single surgeon (*Table 1*).

	Vivanta	**Arnica/Bromelain**
Number of patients	130	80
Age (Mean)	47.3	45.8
Sex	130 Female: 0 Male	80 Female: 0 Male

Table 1: Patient demographics.

Narcotic use was normalized to 1mg morphine equivalents. In the post-operative recovery period, patients supplemented with Vivanta required 41% less narcotic that those supplemented with arnica and bromelain. This trend continued upon discharge with Vivanta patients using 25% less Tylenol with codeine than their counterparts (*Table 2*), with the Vivanta group also reporting a faster reduction in pain scores (*Figure 2*).

There was a dramatic reduction of post-surgical drainage in the Vivanta patient group. Patients also reported being able to function independently approximated 2 days earlier when supplemented with Vivanta.

Outcomes (Mean values)	**Vivanta**	**Arnica/Bromelain**	**Change %**
Recovery Narcotic Use (Morphine Equivalents)	3.85	7.8	41% *
Post-operative Drainage (mL)	144	277	48% **
Home Tylenol #3 Use (# of pills)	12.89	17.25	25% *
Days to Independent Activity	3.5	5.6	37% **

Key: * P<0.001, ** p<0.05

Table 2: Results of measured outcomes.

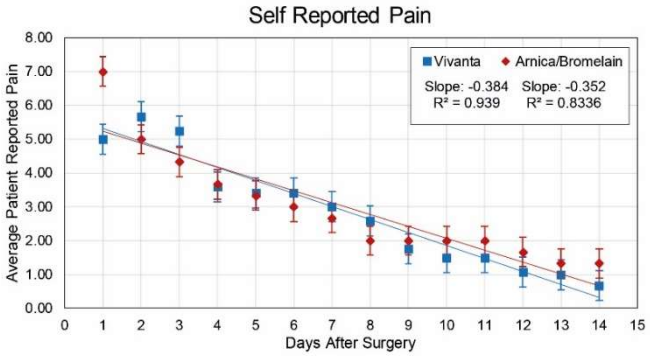

Figure 3: Rate of decrease in patient reported pain. Rate of change is approximately 10% faster for Vivanta.

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 hospital length of stay when given perioperatively [10,14-25]. The mechanistic action of arginine, citrulline and glutamine center around their roles in nitric oxide production and the role nitric oxide mediation of various metabolic pathways [2-6]. Nitric oxide mediates host immune defense [2,3,30] while also exhibiting protective effects on the cardiovascular system by acting as a vasodilator [31]. 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 [2] but the natural glutamine-citrulline-arginine pathway can be impaired after surgical trauma [31]. 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 [12,13]. The combination of these two factors requires an exogenous source of arginine to correct [10-13], as deficiencies can lead to immunosuppression, impaired recovery and altered vascular function [3,6]. 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 [1,4]. Tissue ischemia, induced by surgical trauma causes an anaerobic cellular metabolism, leading to acidosis, as well as decreased cellular glycogen and ATP levels that cause reduced cell membrane function, vascular endothelial adhesions, and an upregulation of clotting pathways [2,33]. 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 [34,35]. This ischemia-reperfusion process diminishes cell function and impairs wound healing. Nitric oxide and glutamine supplementation has been shown to protect against both ischemia-reperfusion injury and further modulate collagen synthesis [2,4,35,36].

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 was the first to show a significant reduction of pain and narcotic requirements.

Reduction in narcotic use

Supplementation with Vivanta reduced narcotic use both in the post-surgical recovery room and after the patient was discharged home (*Table 2)*. A drastic reduction of 41% in morphine equivalents in recovery was observed and a 25% reduction in Tylenol #3 use upon the two weeks of home recovery. Patients self-assessed pain who took Vivanta also decreased on average 10% faster than the arnica/bromelain group (*Figure 3)*. Most patients in the Vivanta group stopped taking Tylenol #3 after three days, indicated 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 as the compounds in Vivanta have no analgesic properties. We would hypothesize that the supplementation with Vivanta 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 a synergistic 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 this data highly subjective.

Future work

As 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. Vivanta reduced recovery narcotic use by 41%, post-operative drainage by 48% and home Tylenol #3 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.

References

[1] Martin P, Nunan R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. Br J Dermatol. 2015;173(2):370-8.

URL: https://www.ncbi.nlm.nih.gov/pubmed/26175283

[2] Witte MB, Barbul A. Role of nitric oxide in wound repair. Am J Surg. 2002;183(4):406-12.

URL: https://www.ncbi.nlm.nih.gov/pubmed/11975928

[3] Nieves C, Langkamp-henken B. Arginine and immunity: a unique perspective. Biomed Pharmacother. 2002;56(10):471-82.

URL: https://www.ncbi.nlm.nih.gov/pubmed/12504268

[4] Schaffer MR, Tantry U, Gross SS, Wasserburg HL, Barbul A. Nitric oxide regulates wound healing. J Surg Res. 1996;63(1):237-40.

URL: https://www.ncbi.nlm.nih.gov/pubmed/8661204

[5] Shi HP, Most D, Efron DT, Witte MB, Barbul A. Supplemental L-arginine enhances wound healing in diabetic rats. Wound Repair Regen. 2003;11(3):198-203.

URL: https://www.ncbi.nlm.nih.gov/pubmed/12753601

[6] Wu G, Bazer FW, Davis TA, et al. Arginine metabolism and nutrition in growth, health and disease. Amino Acids. 2009;37(1):153-68.

URL: https://www.ncbi.nlm.nih.gov/pubmed/19030957

[7] Morris SM. Arginine: beyond protein. Am J Clin Nutr. 2006;83(2):508S-512S.

URL: https://www.ncbi.nlm.nih.gov/pubmed/16470022

[8] Suzuki T, Morita M, Hayashi T, Kamimura A. The effects on plasma L-arginine levels of combined oral L-citrulline and L-arginine supplementation in healthy males. Biosci Biotechnol Biochem. 2017;81(2):372-375.

URL: https://www.ncbi.nlm.nih.gov/pubmed/27667025

[9] Williams JZ, Abumrad N, Barbul A, Effects of a specialized amino acid mixture on human collagen deposition. Ann. Surg. 2002; 236(3): 369-375.

URL: https://www.ncbi.nlm.nih.gov/pubmed/12192323

[10] 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(3):F567-75.

URL: https://www.ncbi.nlm.nih.gov/pubmed/27194717

[11] Morris SM. Arginine metabolism: boundaries of our knowledge. J Nutr. 2007;137(6 Suppl 2):1602S-1609S.

URL: https://www.ncbi.nlm.nih.gov/pubmed/17513435

[12] Vissers YL, Dejong CH, Luiking YC, Fearon KC, Von meyenfeldt MF, Deutz NE. Plasma arginine concentrations are reduced in cancer patients: evidence for arginine deficiency?. Am J Clin Nutr. 2005;81(5):1142-6.

URL: https://www.ncbi.nlm.nih.gov/pubmed/15883440

[13] 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(4):328-34.

URL: https://www.ncbi.nlm.nih.gov/pubmed/3923266

[14] Marik PE, Flemmer M. Immunonutrition in the surgical patient. Minerva Anestesiol. 2012;78(3):336-42.

URL: https://www.ncbi.nlm.nih.gov/pubmed/22240611

[15] Brinkmann S. Preoperative oral nutritional interventions in surgery, including arginine- and glutamine-enhanced supplements. *CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources*. 2013;8(015).

URL:https://www.researchgate.net/publication/236153155_Preoperative_oral_nutritional_interventions_in_surgery_including_arginine-_and_glutamine-enhanced_supplements

[16] Wachtler P, Axel hilger R, König W, Bauer KH, Kemen M, Köller M. Influence of a pre-operative enteral supplement on functional activities of peripheral leukocytes from patients with major surgery. Clin Nutr. 1995;14(5):275-82.

URL: https://www.ncbi.nlm.nih.gov/pubmed/16843943

[17] 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(9130):772-6.

URL: https://www.ncbi.nlm.nih.gov/pubmed/9737282

[18] Wischmeyer PE, Dhaliwal R, Mccall M, Ziegler TR, Heyland DK. Parenteral glutamine supplementation in critical illness: a systematic review. Crit Care. 2014;18(2):R76.

URL: https://www.ncbi.nlm.nih.gov/pubmed/24745648

[19]Avenell A. 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(3):261-8.

URL: https://www.ncbi.nlm.nih.gov/pubmed/19490739

[20] 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(2):213-23.

URL: https://www.ncbi.nlm.nih.gov/pubmed/23196117

[21] Sacks GS, Genton L, Kudsk KA. Controversy of immunonutrition for surgical critical-illness patients. Curr Opin Crit Care. 2003;9(4):300-5.

URL: https://www.ncbi.nlm.nih.gov/pubmed/12883285

[22] 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(12):1309-16.

URL: https://www.ncbi.nlm.nih.gov/pubmed/10593328

[23] Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr. 2006;25(2):224-44.

URL: https://www.ncbi.nlm.nih.gov/pubmed/16698152

[24] 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(5):506-13.

URL: https://www.ncbi.nlm.nih.gov/pubmed/23635587

[25] Debats IB, Wolfs TG, Gotoh T, Cleutjens JP, Peutz-kootstra CJ, Van der hulst RR. Role of arginine in superficial wound healing in man. Nitric Oxide. 2009;21(3-4):175-83.

URL: https://www.ncbi.nlm.nih.gov/pubmed/19638312

[26] 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(3):e21019.

URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4884440/

[27] 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;41:813-7.

URL: https://www.ncbi.nlm.nih.gov/pubmed/13987821

[28] 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(6):1043-8.

URL: https://www.ncbi.nlm.nih.gov/pubmed/24589242

[29] Brito N, Knipschild P, Doreste-Alonso J. Systematic Review on the Efficacy of Topical Arnica montana for the Treatment of Pain, Swelling and Bruises. *Journal of Musculoskeletal Pain*. 2014;22(2):216-223

URL: https://doi.org/10.3109/10582452.2014.883012

[30] Iuvone T, Van osselaer N, D'acquisto F, Carnuccio R, Herman AG. Differential effect of L-NAME and S-methyl-isothiourea on leukocyte emigration in carrageenin-soaked sponge implants in rat. Br J Pharmacol. 1997;121(8):1637-44.

URL: https://www.ncbi.nlm.nih.gov/pubmed/9283697

[31] Barbul A, Lazarou SA, Efron DT, Wasserkrug HL, Efron G. Arginine enhances wound healing and lymphocyte immune responses in humans. Surgery. 1990;108(2):331-6.

URL: https://www.ncbi.nlm.nih.gov/pubmed/2382229

[32] Vermeulen MA, Van de poll MC, Ligthart-melis GC, et al. Specific amino acids in the critically ill patient--exogenous glutamine/arginine: a common denominator?. Crit Care Med. 2007;35(9 Suppl):S568-76.

URL: https://www.ncbi.nlm.nih.gov/pubmed/17713411

[33] Aivatidi C, Vourliotakis G, Georgopoulos S, Sigala F, Bastounis E, Papalambros E. Oxidative stress during abdominal aortic aneurysm repair--biomarkers and antioxidant's protective effect: a review. Eur Rev Med Pharmacol Sci. 2011;15(3):245-52.

URL: https://www.ncbi.nlm.nih.gov/pubmed/21528769

[34] 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(1):80-6.

URL: https://www.ncbi.nlm.nih.gov/pubmed/22981497

[35] Zhang WX, Zhou LF, Zhang L, et al. Protective effects of glutamine preconditioning on ischemia-reperfusion injury in rats. HBPD INT. 2011;10(1):78-82.

URL: https://www.ncbi.nlm.nih.gov/pubmed/21269939

[36] Sessa WC. Molecular control of blood flow and angiogenesis: role of nitric oxide. J Thromb Haemost. 2009;7 Suppl 1:35-7.

URL: https://www.ncbi.nlm.nih.gov/pubmed/1963076