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Research Article

Papaverine Shortage: Verapamil-Nitroglycerin Solution as a Substitute

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Abstract

Objective: Papaverine is a topical agent commonly used during microvascular surgery to inhibit undesired vasoconstriction. There is a national shortage of papaverine due to ceased production by the only manufacturer within the United States. Establishment of an alternative vasodilator is critically important. This study aims to assess the experience of a solution of verapamil and nitroglycerin (VG solution), a potentially suitable alternative pharmacologic vasodilator.

Study Design: Retrospective chart review

Methods: 188 consecutive free flaps were performed for head and neck defect reconstruction between February 11, 2013 and February 28, 2015. The topical vasodilator of VG solution was used during these cases. Charts were reviewed for patient and flap characteristics, intraoperative patient and flap complications, and postoperative complications.

Results: Flaps performed (n=188) included fibula, radial forearm, subscapular system, anterolateral thigh, and rectus abdominis. There were no vascular thromboses or free flap failures, and one patient with hematoma formation. Specific to topical application of the VG solution, there were no intraoperative cardiac events or abnormalities secondary to application of the solution, including obvious endothelial damage or irreversible arterial vasospasm. No vessels demonstrated intraoperative vasospasm after VG solution application.

Conclusion: Use of a VG solution for pharmacological vasodilation during microvascular free tissue transfer did not result in any adverse events and an acceptable vasodilation was witnessed, yielding a potentially acceptable papaverine substitute.

ABBREVIATIONS

VG: Verapamil-Nitroglycerin

INTRODUCTION

Papaverine hydrochloride is a topical phosphodiesterase inhibitor commonly used during microvascular surgery. Although its mechanism of action is not entirely understood, its application helps prevent or reduce arterial spasm, facilitating vessel anastomosis by increasing vessel circumference. Subsequent vasospastic complications are also theoretically reduced. These benefits have promoted the use of papaverine during microvascular surgery [1].

A recent national shortage of papaverine has deprived many centers of the use of this important aid to successful microvascular surgery [2-4]. Until recently, papaverine was manufactured in the United States by Ely Lilly and Company (Indianapolis, IN) and by American Regent (Shirley, NY). Ely Lilly and Company exited the marketplace, leaving American Regent as the sole manufacturer of papaverine. The current shortage is due to a manufacturing facility change at American Regent. The timeline for restoration of adequate manufacturing supply of papaverine in the United States remains uncertain. Given the current and possible long-term shortage, development of an alternative vasodilator for use during microvascular surgery is critically important.

Literature and experience within cardiothoracic surgery supports the use of a verapamil -glyceryl trinitrate (an alternative name for nitroglycerin) (VG) solution, which is commonly

used in coronary artery bypass graft (CABG) surgery. We have adopted this compound for use during microvascular surgery. Additionally, this solution appears to have decreased endothelial cytotoxicity than other commonly used solutions, including papaverine or lidocaine [5].

The current world literature of microvascular surgery lacks clinical data of a robust alternative to papaverine. We present our experience with this alternative antispasmodic solution by examining any potential adverse events due to its use. We hope our experience aids other microvascular surgeons in easily establishing and adopting an alternative to papaverine.

MATERIALS AND METHODS

The University of California Los Angeles Institutional Review Board approved this retrospective chart review. The hospital pharmacy exhausted its supply of papaverine and shifted to a combination of VG solution on February 11, 2013. A retrospective chart review was completed of 188 consecutive free flaps in which the new drug combination was utilized. Free flaps performed between February 11, 2013 and February 28, 2015 were assessed. All patients had a minimum of one-month follow-up in order to assess postoperative outcomes.

Data reviewed included operative notes, anesthesia records, discharge summaries, and postoperative hospital and clinic notes. Variables collected included age, gender, flap characteristics, choice of recipient vessels, intraoperative patient and flap complications, and postoperative complications. A descriptive analysis was performed.

Intraoperatively, the nitroglycerin and verapamil solution is applied to the vessel using a 25-gauge anterior chamber blunt needle on a 3mL syringe. All administrations were topical and the solution was not instilled intravascularly. Specifically, the blunt needle was gently pressed against the exterior of the vessel wall and small aliquots of solution were delivered to the vessel adventitia. VG solution was routinely applied after dissection and preparation of the recipient artery prior to microvascular anastomosis. At the commencement of microvascular anastomosis, the solution was re-applied to the recipient and flap artery and vein(s) surrounding the anastomosis.

The utilized VG solution is mixed in the operating room by the nursing staff (Table 1). The nitroglycerin concentration can be composed with either (1) a nitroglycerin stick (0.1mg/mL), (2) nitroglycerine 0.1mg/mL solution, (3) mixing 0.5mL of nitroglycerin (5mg/mL) into a 50mL bag of 5% Dextrose injection USP, or (4) mixing 0.2mL of nitroglycerin (5mg/mL) in 9.8mL 5% Dextrose injection USP.

RESULTS

A total 188 consecutive patients underwent free flap surgery for reconstruction of head and neck defects. Intraoperative use of VG solution was utilized in all patients by the pervious outlined method.

Table 2 summarizes the clinical characteristics of these patients. Males accounted for 119 (63.3%) of the patients. The mean patient age was 62.7 years (range 13-94 years). Patients most commonly underwent fibular osteocutaneous (n=76), radial forearm (n=66), and anterolateral thigh (n=33) free flap reconstructions following head and neck extirpative surgery.

Table 1: VG Solution.

Component	Volume
Nitroglycerin 0.1 mg/mL*	10mL
Verapamil 2.5 mg/mL	4mL
Sodium chloride 0.9%	16mL

*Alternatives constitution of nitroglycerin provided in Methods.

Table 2: Patient Demographics and Outcomes.

	Total Patients (n=188)
Patient Characteristic	
Males, n (%)	119 (63.3%)
Age (years), average (SD)	62.7 (14.8)
Flap Type, n (%)	
Fibula	76 (40.4%)
Radial Forearm	66 (35.1%)
Anterolateral Thigh	33 (17.6%)
Subscapular System	12 (6.4%)
Rectus abdominus	1 (0.5%)
Recipient Artery Characteristics	
Total arterial anastomosis, n*	189
Recipient artery	
Facial, n (%)	150 (79.4%)
Lingual, n (%)	24 (12.7%)
Terminal external carotid, n (%)	8 (4.2%)
Superficial temporal, n (%)	6 (3.2%)
Transverse cervical, n (%)	1 (0.5%)
Recipient Vein Characteristics	
Total venous anastomosis, n	248
Double vein anastomosis, n (%)	60 (31.9%)
Recipient vein	
External jugular vein, n (%)	140 (56.5%)
Common facial vein, n (%)	73 (29.4%)
Internal jugular vein, n (%)	25 (10.1%)
Anterior jugular vein, n (%)	5 (2.0%)
Middle thyroid vein, n (%)	3 (1.2%)
Superficial temporal vein, n (%)	1 (0.4%)
Transverse cervical vein, n (%)	1 (0.4%)
Surgical Outcomes, n (%)	
Flap loss	0 (0%)

*One ALT free flap required anastomosis of 2 individual perforators to the facial and superficial temporal arteries.

The most commonly used recipient artery was the facial artery (n=150; 79.4% of cases). Sixty flaps (31.9%) had double venous anastomosis, yielding a total of 248 venous anastomoses. The most frequently used vein was the external jugular vein (56.5%), followed by the common facial vein (29.4%).

No patients developed impaired postoperative flap perfusion, and there were no postoperative free flap failures. One fibula free flap did require intravascular alteplase (Genentech, South San Francisco, California) in addition to topical VG solution due to appearance of limited arterial blood flow immediately after anastomosis, with resultant sustained arterial flow. Another patient developed recurrent hematomas on postoperative days 6, 10 and 29 without identifiable source or etiology.

Specific to topical application of the VG solution, there were no intraoperative cardiac events or abnormalities clearly referable to application of the solution. In no case was there obvious endothelial damage or irreversible arterial vasospasm. Subjectively, the authors noted a desirable robust vasodilatory response of the recipient artery to the topical application of the VG solution. None of the flap pedicles or recipient arteries demonstrated intraoperative vasospasm after VG solution application.

DISCUSSION

Pharmacologic vasodilators are extremely useful agents during microvascular surgery. By offsetting arterial vasospasm, they can directly prevent vascular compromise and therefore free tissue transfer loss. Intraoperative vessel spasm can be attributed to a multitude of factors, including minor surgical manipulative trauma, preoperative and intraoperative medication administration, fluctuations in body temperature, and endogenous catecholamine release. Additionally, venospasm similarly occurs due to mechanical factors that stimulate contraction of smooth muscle [6,7]. In this report, we describe the use of a VG solution as a vasodilator in 188 consecutive free flaps, and we encountered no adverse events. This solution has not been previously described for use in microvascular surgery.

Vasospasm may negatively affect microsurgical outcomes by two primary mechanisms. First, it may decrease the perfusion pressure and may lead to free flap compromise. More commonly, vasospasm-induced narrowing increases the technical difficulty of suture placement during anastomosis. Narrow diameter vessels carry an inherently increased likelihood of unintentional incorporation of the vessel back-wall into a suture needle pass [7]. Additionally, narrow diameter vessels have an increased risk of thrombotic potential due to a smaller cross sectional area. For these reasons, narrow diameter vessels have been well established to correlate with increased technical difficulty and increased rate of flap failure [8,9].

To counter the negative effects of vasospasm and to optimize flap success rates, many microsurgeons utilize intraoperative topical pharmacologic vasodilators. Yu et al. conducted a survey of microvascular surgeons in the United Kingdom and showed that 94% utilized pharmacologic vasodilators in their surgical practices. The most commonly used vasodilator in the survey was papaverine (52%), followed by verapamil [7].

In the United States, topical application of papaverine was commonly used to combat vasospasm of the recipient and flap vessels. Papaverine was first used in surgery by Green in 1971 on the internal mammary artery, [10] and many of the subsequent studies examining its effect on vessels come from the cardiothoracic literature. Papaverine is a nonspecific vasodilator substance and its exact mechanism of action is not fully understood. It is a phospohodiesterase inhibitor and may raise cyclic guanosine 5'-monophosphate (cGMP) levels in smooth muscle cells. Additionally, it may decrease calcium influx or inhibit the release of intracellular calcium stores. Topically administered at high concentrations on a vessel, it produces a dilatational effect [5,6]. However, papaverine solution used intraoperatively is highly acidic (pH 4.4), and in nonacidic solutions papaverine hydrochloride is relatively unstable with formation of a possible white precipitate. Intraluminal administration of papaverine has been shown to cause endothelial damage [5,11].

A commonly used alternative to papaverine is lidocaine solution. Kirschner and Futran showed that both lidocaine 1% and papaverine were able to produce vasodilation in a rat model. Since the effect of the papaverine was of a longer duration, they concluded it was the superior of the two agents [1]. Evans et al. showed that lidocaine applied topically to a rabbit carotid artery produced a biphasic response with low concentrations yielding vessel contraction [12]. In a subsequent report, the same group reported higher concentrations of lidocaine (20%) produced vasodilation similar to papaverine in rabbit carotid arteries [13]. Other groups have similarly reported dose-dependent vasoconstriction caused by lidocaine [14,15]. To avoid potential toxicity of high dose lidocaine and given its potential vasoconstrictive properties, our group chose not to use lidocaine as a substitute for papaverine.

Multiple studies in the cardiac surgery literature describe the use of VG solution as a favorable alternative to papaverine due to a longer duration of action and lower potential for endothelial damage, as described previously [5,11,16]. First introduced in 1993 by He and associates, VG solution is primarily a mixture of verapamil and nitroglycerin [17,18]. Verapamil blocks calcium influx and subsequently smooth muscle cell contractility by selective blockade of L-type voltage-operated calcium channels, while nitroglycerin releases nitric oxide into the muscle cell stimulating cGMP release. The synergistic effects of these two mechanisms can effectively reverse vascular spasm of any etiology, receptor-mediated or depolarization-mediated, including adrenergic, thromboxane, prostanoid, and angiotensin mediated vasoconstriction [6,19,20]. VG solution has a shorter latency than papaverine, as vessel relaxation occurs within ten minutes of application [19]. Additionally, VG solution's five hour duration of action is significantly longer than the one hour effectiveness of papaverine [16].

A significant limitation of this report is the lack of objective measurements of arterial vasodilation after application of the VG solution. These could include vessel diameter and blood flow rate. Additionally, comparative assessment of VG solution to control or papaverine is not provided. This information will be provided through upcoming studies from our group. Instead, at this time, we find it may be most useful to communicate the VG solution to our reconstructive colleagues who may be facing similar issues with establishing a reliable vasodilator substitute. In particular, we show that the solution is safe for application, warranting further study of drug efficacy.

CONCLUSION

Given a shortage of papaverine in the United States since

2013, microvascular surgeons without access to the drug have had to adopt an alternate intraoperative topical vasodilator. We describe and establish the use of a VG solution for microvascular free tissue transfer. In our experience of using this solution in 188 consecutive free flaps, we have not encountered any adverse events and there were no flap failures. Subjectively, application of the VG solution created an acceptable vasodilation similar to that experienced previously with papaverine. Further, due to potential endothelial damage from papaverine, our practice has shifted to use of VG solution despite any potential return of papaverine.

REFERENCES

1. Kerschner JE, Futran ND. The effect of topical vasodilating agents on microvascular vessel diameter in the rat model. Laryngoscope. 1996; 106: 1429-1433.
2. Blackwell KE. Unsurpassed reliability of free flaps for head and neck reconstruction. Arch Otolaryngol Head Neck Surg. 1999; 125: 295-299.
3. Suh JD, Sercarz JA, Abemayor E, Calcaterra TC, Rawnsley JD, Alam D, et al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg. 2004; 130: 962-966.
4. Nuara MJ, Sauder CL, Alam DS. Prospective analysis of outcomes and complications of 300 consecutive microvascular reconstructions. Arch Facial Plast Surg. 2009; 11: 235-239.
5. Formica F, Ferro O, Brustia M, Corti F, Colagrande L, Bosisio E, et al. Effects of papaverine and glycerylnitrate-verapamil solution as topical and intraluminal vasodilators for internal thoracic artery. Ann Thorac Surg. 2006; 81: 120-124.
6. Attaran S, John L, El-Gamel A. Clinical and potential use of pharmacological agents to reduce radial artery spasm in coronary artery surgery. Ann Thorac Surg. 2008; 85: 1483-1489.
7. Yu JT, Patel AJ, Malata CM. The use of topical vasodilators in microvascular surgery. J Plast Reconstr Aesthet Surg. 2011; 64: 226-228.
8. Khouri RK. Avoiding free flap failure. Clin Plast Surg. 1992; 19: 773-781.
9. Khouri RK, Cooley BC, Kunselman AR, Landis JR, Yeramian P, Ingram D, et al. A prospective study of microvascular free-flap surgery and outcome. Plast Reconstr Surg. 1998; 102: 711-721.
10. Green GE. Rate of blood flow from the internal mammary artery. Surgery. 1971; 70: 809-813.
11. He GW. Verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with papaverine solution. J Thorac Cardiovasc Surg. 1998; 115: 1321-1327.
12. Evans GR, Gherardini G, Gürlek A, Langstein H, Joly GA, Cromeens DM, et al. Drug-induced vasodilation in an in vitro and in vivo study: the effects of nicardipine, papaverine, and lidocaine on the rabbit carotid artery. Plast Reconstr Surg. 1997; 100: 1475-1481.
13. Gherardini G, Gürlek A, Cromeens D, Joly GA, Wang BG, Evans GR. Drug-induced vasodilation: in vitro and in vivo study on the effects of lidocaine and papaverine on rabbit carotid artery. Microsurgery. 1998; 18: 90-96.
14. Johns RA, DiFazio CA, Longnecker DE. Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. Anesthesiology. 1985; 62: 141-144.
15. Jernbeck J, Samuelson UE. Effects of lidocaine and calcitonin gene-related peptide (CGRP) on isolated human radial arteries. J Reconstr Microsurg. 1993; 9: 361-365.
16. Mussa S, Guzik TJ, Black E, Dipp MA, Channon KM, Taggart DP. Comparative efficacies and durations of action of phenoxybenzamine, verapamil/nitroglycerin solution, and papaverine as topical antispasmodics for radial artery coronary bypass grafting. The Journal of Thoracic and Cardiovascular Surgery. 2003; 126: 1798-1805.
17. He GW, Buxton BF, Rosenfeldt FL, Angus JA, Tatoulis J. Pharmacologic dilatation of the internal mammary artery during coronary bypass grafting. J Thorac Cardiovasc Surg. 1994; 107: 1440-1444.
18. He GW, Rosenfeldt FL, Angus JA. Pharmacological relaxation of the saphenous vein during harvesting for coronary artery bypass grafting. Ann Thorac Surg. 1993; 55: 1210-1217.
19. He GW, Yang CQ. Use of verapamil and nitroglycerin solution in preparation of radial artery for coronary grafting. Ann Thorac Surg. 1996; 61: 610-614.
20. He GW, Yang CQ, Starr A. Overview of the nature of vasoconstriction in arterial grafts for coronary operations. Ann Thorac Surg. 1995; 59: 676-683.

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