International Journal of Research in Medical Sciences
Shah SD et al. Int J Res Med Sci. 2025 May;13(5):1942-1946
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20251292

Original Research Article

The role of topical papaverine in microvascular surgery

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Received: 05 March 2025
Revised: 08 April 2025
Accepted: 19 April 2025

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ABSTRACT

Background: Intraoperative vasospasm during microvascular surgery can significantly impact surgical outcomes, leading to reduced blood flow and potential flap failure. This study evaluates the effects of local application of topical Papaverine, a nonspecific phosphodiesterase inhibitor, in enhancing vessel diameter, preventing vasospasm, and improving flap survival. A total of 1,000 microvascular anastomoses were analysed across multiple reconstruction types. Results showed an average of 66% increase in arterial diameter, reduced incidence of thrombus formation, and improvement in flap survival rates. Papaverine demonstrated immediate vasodilatory effects, solidifying its role as a gold-standard agent in microsurgery.

Methods: A retrospective study evaluated 1,000 microvascular anastomoses performed in a single year. reconstruction such as head and neck, post-oncological, extremity, and digital re-implantations were included. Papaverine was sprayed topically over vessels. Vessel diameter changes were measured before and 10 minutes after application.

Results: Significant improvement in vessel diameter following Papaverine application. Arterial diameter increased by an average of 66%, while venous dilation was observed at a 23% increase. Papaverine's strong vasodilatory effects, particularly in arteries with higher smooth muscle content. The rapid onset of action (within 1–5 minutes) was consistent, ensuring immediate resolution of vasospasm. overall flap survival rate improved by 15%, and re-exploration rates decreased from 8% to 3%, emphasizing its role in enhancing surgical outcomes.

Conclusions: Papaverine effectively prevents intraoperative vasospasm, enhances vessel diameter, and improves overall flap survival by reducing re exploration rates. These findings validate its role as a gold-standard vasodilator in microvascular surgery.

Keywords: Papaverine, Microvascular surgery, Vasospasm prevention, Vessel diameter, Flap survival

INTRODUCTION

Intraoperative vasospasm, caused by direct vascular manipulation, metabolic imbalances, or intrinsic factors, poses a risk of flap compromise in microvascular surgery. Persistent vasospasm occurs in 5-10% of cases, potentially resulting in partial or complete flap loss. Papaverine, a nonspecific phosphodiesterase (PDE) inhibitor and opium alkaloid, relaxes vascular smooth muscle cells (VSMCs) by increasing intracellular cyclic guanosine monophosphate (cGMP). Its vasodilatory and antispasmodic properties, along with its ability to inhibit platelet aggregation, make it an essential tool in microvascular surgery. The mechanism underlying vasospasm during the procedure is complex and can occur in response to various stimuli. This response includes direct manipulation of blood vessels, metabolic homeostasis, and inherent tendencies.[1-9] Mechanical

stretching of blood vessels can induce muscular reactions and alter the membrane potential. Rapid changes in the membrane potential can induce smooth muscle cell contraction and vasoconstriction. These reactions often occur during the handling and preparation of pedicles. Proper management of vascular dissection and minimization of tension is crucial.[2]

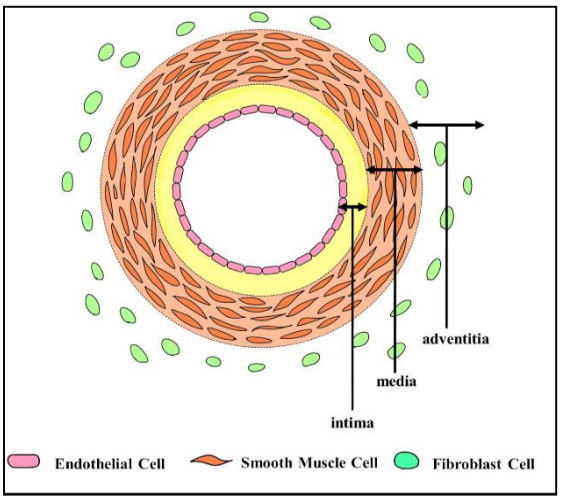

Figure 1: Anatomy of vessel wall.[3-5]

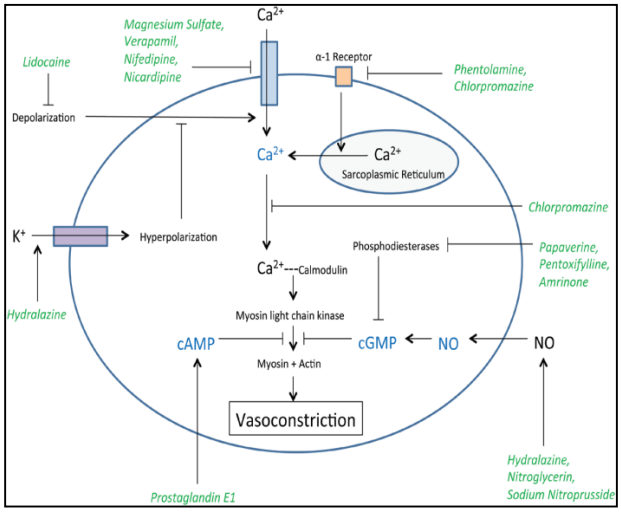

Figure 2: Action of various vasodilator.[1,2,9]

The cellular components of blood vessels play a significant role in these reactions. The arterial wall is anatomically structured into three layers: intima, media, and adventitia.[3] Endothelial cells (ECs) are important constituents of the intima and perform various functions. ECs secrete numerous bioactive substances that regulate vascular tone. The release of substances such as nitric oxide (NO), prostaglandin I2 (PGI2), and endothelium-derived relaxing factor (EDRF), also known as an endothelium-derived hyperpolarizing factor (EDHF), induces local smooth muscle relaxation and subsequent vasodilation. In contrast, paracrine factors such as endothelin-1 and thromboxane A2 induce vasoconstriction. ECs also maintain the smoothness of the intima, prevent platelet and leukocyte adhesion, and protect against the entry of harmful molecules into the arterial vessel wall.[4] The media of blood vessel walls consists of multiple layers of smooth muscle cells (SMCs).[5] SMCs are essential for proper blood vessel function.[6] This study aims to analyze papaverine's efficacy in facilitating anastomoses and enhancing flap survival in diverse reconstructive scenarios.

METHODS

Study design and setting

This was a retrospective observational study conducted at the Department of Burns, Plastic and Reconstructive Surgery, SMT Shardaben Municipal Hospital, Ahmedabad. The study was carried out over a one-year period, from December 2023 to December 2024.

Patient selection criteria

All patients who underwent microvascular free tissue transfer, including head and neck reconstructions post-oncological resection, extremity reconstructions, and digital re-implantations, were included. Patients with incomplete medical records or lost to follow-up within 7 days post-operatively were excluded from the analysis.

Procedure

A total of 1,000 microvascular anastomoses were evaluated. For each case, topical Papaverine was used as a vasodilator to prevent intraoperative vasospasm. The solution was prepared by diluting 2 ml of Papaverine in 8 ml of normal saline. This diluted solution was sprayed directly onto the exposed artery and vein at the site of microvascular anastomosis. The arterial and venous diameters were measured before application and again 10 minutes after topical Papaverine administration using a microsurgical scale Flap perfusion was continuously monitored intraoperatively and postoperatively through clinical indicators including color, temperature, and capillary refill. The rates of flap survival, re-exploration, and vessel thrombosis were recorded.

Ethical approval

This study was conducted in accordance with institutional ethical standards. As it was a retrospective study utilizing anonymized data, formal ethical committee approval was not required.

Statistical analysis

Quantitative data such as vessel diameters were reported as mean and standard deviation (SD). Categorical variables including flap survival and re-exploration rates were presented as numbers and percentages. Data were analyzed using basic descriptive statistics through

Microsoft Excel. Given the descriptive nature of the study, no inferential statistical tests were applied.

RESULTS

The study demonstrated a significant improvement in vessel diameter following Papaverine application. Arterial diameter increased by an average of 66% (from 1.5 mm to 2.5 mm), while venous dilation was observed at a 23% increase (from 2.46 mm to 3.02 mm).

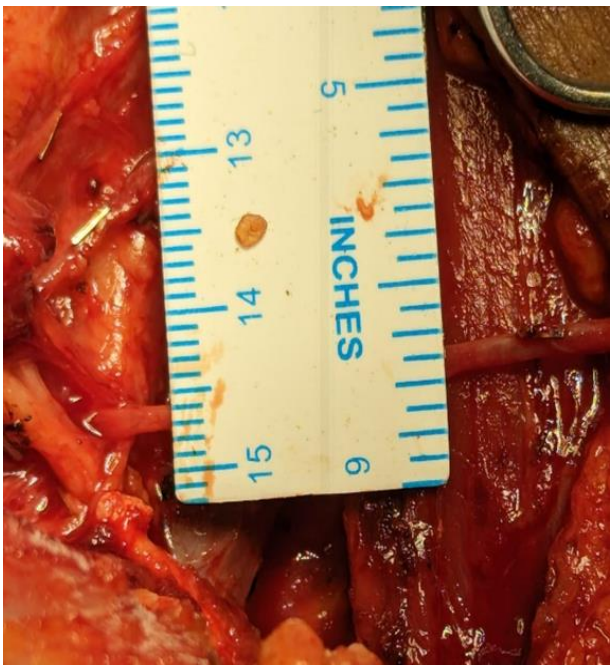

Figure 3: Before application of Papaverine.

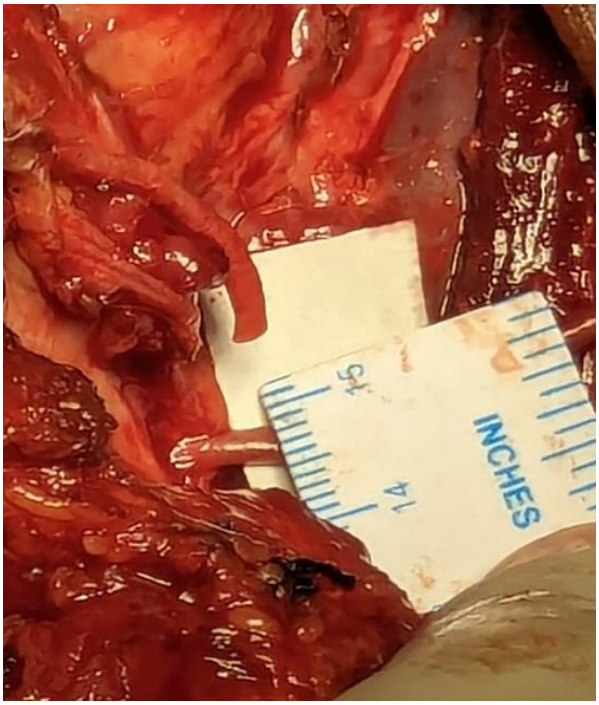

Figure 4: Dilatation of vessel after topical application.

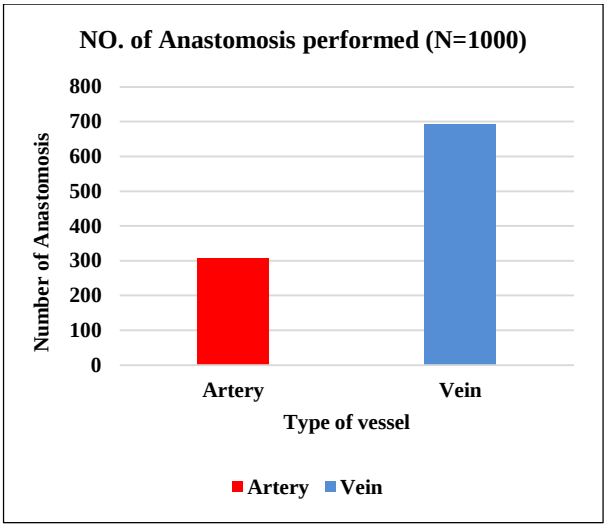

Figure 5: Number of vessel anastomosis.

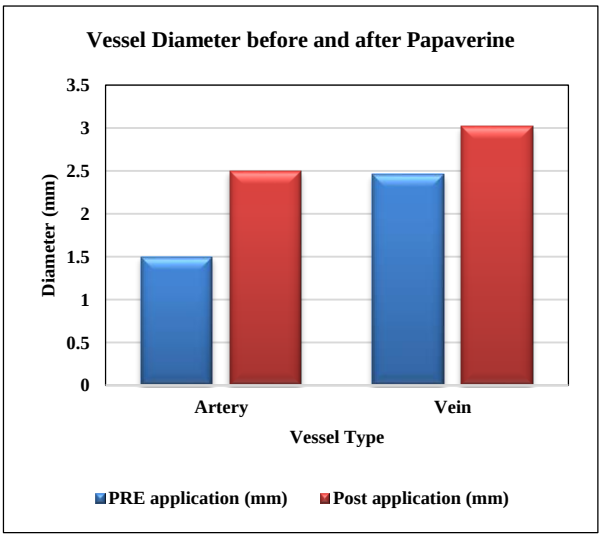

Figure 6: Vessel diameter before and after Papaverine.

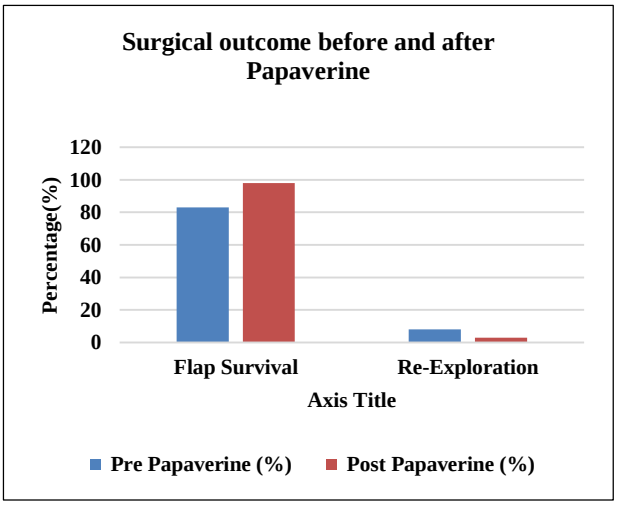

Figure 7: Surgical outcome before and after Papaverine.

Table 1: Numbers of vessel anastomosis performed.

Anastomotic vessel	No. of anastomosis done (n=1000)
Artery	308
Vein	692

Table 2: Vessel diameter changes post application.

Vessel	Pre-application diameter (mm)	Post-application diameter (mm)
Artery	1.5	2.5 (66% increase)
Vein	2.46	3.02 (23% increase)

Table 3: Surgical outcome.

Outcome	Pre papaverine (%)	Post papaverine (%)
Flap survival	83	98
Re- exploration	8	3

Table 4: Participants and surgical characteristics (n=1000).

Characteristics	Number (%) or Mean±SD
Age	45.3±12.7
Gender (male: female) (%)	640 (64%): 360 (36%)
Reconstruction site (%)	
Head and neck	420 (42%)
Extremity	310 (31%)
Digital re implantation	270 (27%)

These findings highlight Papaverine's strong vasodilatory effects, particularly in arteries with higher smooth muscle content. The rapid onset of action (within 1–5 minutes) was consistent across all cases, ensuring immediate resolution of vasospasm. In addition, the overall flap survival rate improved by 15%, and re-exploration rates decreased from 8% to 3%, emphasizing its role in enhancing surgical outcomes.

DISCUSSION

Intraoperative vasospasm remains a frequent challenge during microvascular surgery, particularly during vascular anastomosis, with an incidence reported between 5–10% of cases. Vasospasm can severely compromise flap perfusion, potentially leading to partial or complete flap loss. This study affirms the utility of topical Papaverine as a vasodilatory agent in mitigating intraoperative vasospasm and improving surgical outcomes. Papaverine is a nonspecific phosphodiesterase inhibitor that increases intracellular cGMP and cAMP levels, leading to smooth muscle relaxation and vasodilation. It has demonstrated both antispasmodic and antithrombotic properties.

The findings in our series - a 66% increase in arterial diameter and 23% venous dilation - highlight its strong and rapid action, particularly in arteries, which have thicker muscular walls and are more prone to spasm due to mechanical manipulation. This immediate and consistent vasodilatory effect was observed within 1–5 minutes of application. Arterial responsiveness is attributed to the abundant smooth muscle content in the tunica media, which readily reacts to intracellular signalling changes induced by Papaverine. Veins, having less muscular content, exhibit a lesser but still notable increase in calibre. The improvement in flap survival rate by 15% and the reduction in re-exploration rate from 8% to 3% underscore the clinical significance of effective vasospasm management.

These findings are consistent with Evans et al., who demonstrated improved flow through rabbit carotid arteries post-Papaverine use, and Gherardini et al., who documented its superiority in resolving vasospasm in controlled microsurgical setting.[10] The observed responsiveness in arteries aligns with prior anatomical studies that highlight their thick muscular layer, making them more susceptible to vasospasm and responsive to pharmacological intervention.[5]

Moreover, Huang and Li (2020) validated Papaverine's effectiveness in reversing epinephrine-induced vasospasm, further supporting our clinical findings.[8] In comparative studies, Ricci et al. showed Papaverine outperformed alternatives like lidocaine and calcium channel blockers in restoring microvascular patency.[1] Although agents like nitroglycerin and verapamil have been explored, they often require systemic administration or cause side effects such as hypotension, which Papaverine avoids when used topically.[2]

Our study also contributes real-world, high-volume data from a diverse reconstructive population, supporting Rinkinen and Halvorson's meta-analysis that confirmed Papaverine's frequent use and consistent outcomes across centers.[2]

Nonetheless, cytotoxic effects remain a concern, particularly with high concentrations or prolonged exposure. Studies by Ueda et al. (2023) emphasize the importance of controlled application due to endothelial and smooth muscle toxicity risks.[9]

Limitations

This study is subject to several limitations. First, its retrospective design inherently introduces potential selection and observational biases. Second, it was conducted in a single institution limiting comparisons with patients who did not receive Papaverine. Third, intraoperative blood flow was assessed using vessel diameter measurements rather than objective flow quantification tools like Doppler or fluorescence angiography. Additionally, long-term follow-up to

evaluate flap durability and vascular remodelling was not conducted. Future prospective randomized controlled trials are needed to confirm these findings and establish standardized dosing protocols.

CONCLUSION

Topical papaverine has demonstrated significant efficacy in the prevention and resolution of intraoperative vasospasm during microvascular surgery. By inducing rapid and sustained vasodilation, particularly in arteries, it enhances vessel calibre facilitates smoother anastomosis, and contributes to improved flap viability. The marked reduction in re-exploration rates and the increase in flap survival further underscore its value as a reliable adjunct in microsurgical practice. While its potential cytotoxicity warrants cautious application, Papaverine remains an essential tool in the microsurgical armamentarium, especially in high-stakes reconstructive scenarios.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shah SD, Rajgor DK, Ghelani NB, Godhani CA, Shah VV, Pathak NH. The role of topical papaverine in microvascular surgery. Int J Res Med Sci 2025;13:1942-6.