https://doi.org/10.48047/AFJBS.6.2.2024.3735-3746

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

The Effect of Lidocaine 2% and Magnesium sulphate on Relieving Intraoperative Vasospasm

Yehia Zakaria Awaad Abuelezz , Mohamed Adel Saqr, Ahmed Essam Mohamed

Department of Plastic & Reconstructive Surgery, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Ahmed Essam Mohamed

Email: Ahmedessamelnahas2020@gmail.com

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

doi: 10.48047/AFJBS.6.2.2024.3735-3746

Abstract: Background: Intraoperative microvascular vasospasm occurs in response to numerous stimuli, including direct vascular manipulation, metabolic homeostasis, and intrinsic propensity. Vasospasm can lead to decreased blood flow, stasis, or anastomotic clotting; persistent vasospasm may lead to partial or even complete loss of the microvascular reconstruction. Several factors have been implicated in inducing vasospasm including cold temperature, traction on the vessel wall, bleeding, increased sympathetic tone, and circulating vasoconstrictors. There are no published management algorithms for postoperativemicrovascular arterial vasospasmand the underlying etiology behind this phenomenon has not been clearly elucidated. However, the majority of microsurgeons have encountered this problem at some point in their practice. There are two surgical fields that aremore familiarwith the phenomenon of postoperative arterial vasospasm—cardiac surgery and neurosurgery. A total of 20 articles were included, representing data on 14 vasodilator agents. Drugs not amenable to local intraoperative administration or not approved for clinical use in the United States were excluded. Agents were classified into five pharmacologic categories based on their primary mechanisms: phosphodiesterase inhibitors (papaverine, pentoxifylline, and amrinone), local anesthetics (lidocaine), calcium channel blockers (nicardipine, verapamil, nifedipine, and magnesium sulfate), direct vasodilators (sodium nitroprusside, prostaglandin E1, nitroglycerin, and hydralazine), and alpha antagonists (phentolamine and chlorpromazine). A simplified summary of the mechanisms of action of topical vasodilators on vascular smooth muscle cells

Keywords: *Intraoperative Vasospasm, management*

Introduction

Intraoperative microvascular vasospasm occurs in response to numerous stimuli, including direct vascular manipulation, metabolic homeostasis, and intrinsic propensity. Vasospasm can lead to decreased blood flow, stasis, or anastomotic clotting; persistent vasospasm may lead to partial or even complete loss of the microvascular reconstruction. [1]

Although the inciting mechanism of vasospasm during microsurgery is unclear, it is estimated to significantly affect 5 percent to 10 percent of procedures. Many pharmacologic agents to prevent or reduce vasospasm have been evaluated in animal and in vitro models, although few trials have been performed in a controlled fashion

or on clinical subjects. As a result, plastic surgeons have developed their own criteria and indications for use of vasodilator [2].

A recent survey of plastic surgeons in the United Kingdom revealed that although 94 percent routinely used vasodilators intraoperatively, justification for their use, the agent(s) of choice, and technique of administration varied widely. Papaverine, verapamil, and/or lidocaine were the preferred agents; 99 percent of surgeons used these topically, with 19 percent additionally irrigating the vessel lumen. The majority of surgeons did not know the dose or concentration of the agents they used. [3]

Vasospasm is a common complication in microsurgery that has a deleterious effect on flap blood flow. It occurs more frequently intraoperatively and can rarely occur in the postoperative period. [4]

Several factors have been implicated in inducing vasospasm including cold temperature, traction on the vessel wall, bleeding, increased sympathetic tone, and circulating vasoconstrictors. There are no published management algorithms for postoperativemicrovascular arterial vasospasmand the underlying etiology behind this phenomenon has not been clearly elucidated. However, the majority of microsurgeons have encountered this problem at some point in their practice. There are two surgical fields that aremore familiarwith the phenomenon of postoperative arterial vasospasm—cardiac surgery and neurosurgery. [5]

There is essentially no data regarding the pathophysiology of delayed vasospasm as described in the case report cited below. Given the paucity of published data regarding current practices in dealing with this problem, the authors conducted a survey of reconstructive microsurgeons to elicit their collective experience and thoughts regarding this entity, the results of which A study present below. A study also present a case report from own experience that illustrates the issue and which spurred this current investigation, as well as the background knowledge regarding the delayed vasospastic phenomenon. [6]

Correlation

Arterial vasospasm results from a strong contraction of the smooth muscles in the tunica media leading to narrowing of the vessel lumen and decreased blood flow. This contraction is triggered by calcium influx from intracellular stores, which results from various chemical agent–receptor interactions at the cellular level. Several potential causes of vasospasm have been confirmed in the literature including circulating vasoconstrictors such as catecholamines, physical manipulation of the blood vessel, intimal endothelial injury, and inflammatory mediators. [7]

The effect of physical manipulation is frequently encountered intraoperatively by microsurgeons and is managed by reducing trauma to the vessel wall, minimizing exposure, topical vasodilators, and adventitial stripping. Postoperative arterial vasospasm is a less understood phenomenon with an unclear trigger. There is no high-quality data to explain why vasospasm would occur in a delayed fashion and how best to manage it in a microsurgical setting. [8]

Postoperative arterial vasospasm is well-described and documented in cardiac and neurological surgery, where irreversible and life-threatening consequences may result. Vasospasm in these cases is managed differently from that encountered in microsurgical free tissue transfer, with the mainstay of therapy being intraluminal injection of vasodilating agents via angiography and/or the administration of systemic vasodilators. In microsurgical free tissue transfer surgery, compromise in flap perfusion is usually managed by operative exploration of the vascular pedicle for both diagnosis and treatment. [9]

Recently, indocyanine green angiography has been shown to be of substantive value for monitoring flap perfusion, postoperatively, whenever there is a strong suspicion for vasospasm, especially with intermittent ischemia. Definitive treatment may still require exploration and revision of the anastomosis. Errors in surgical technique (intimal tears, poor suturing technique, rough handling of the vessels) and the mechanical stress (tension or kinking of pedicle) inflicted on the vessels clearly precipitate vasospasm. [10].

Therefore, the question that presents itself in the setting of postoperative arterial vasospasm is whether there is an injured or dysfunctional segment of the vessel. It seems that when a vasospasm etiology is established in postoperative perfusion compromise, particular attention should be paid to the possibility of subtle injury to

the vessel wall. Failure to recognize an injured segment will most likely result in persistence of the problem and return to the OR. [11]

The main clinical question that the authors aimed to address with this study is whether segmental vessel resection is indicated to treat vasospasm, and if so, is it effective? A study are presenting below, with four take backs of a DIEP flap for clinically apparent arterial compromise, with each take back showing marked spasm of the recipient vessel. However, there was some thrombus found in three of the four re-explorations. 18 Over 50% of the surgeon respondents in this series employed some type of vessel resection—whether trimming the vessel ends (61%) or segmental resection of the donor (50%) or recipient vessels (62%), and selective use of venous interposition grafts (42%). [12]

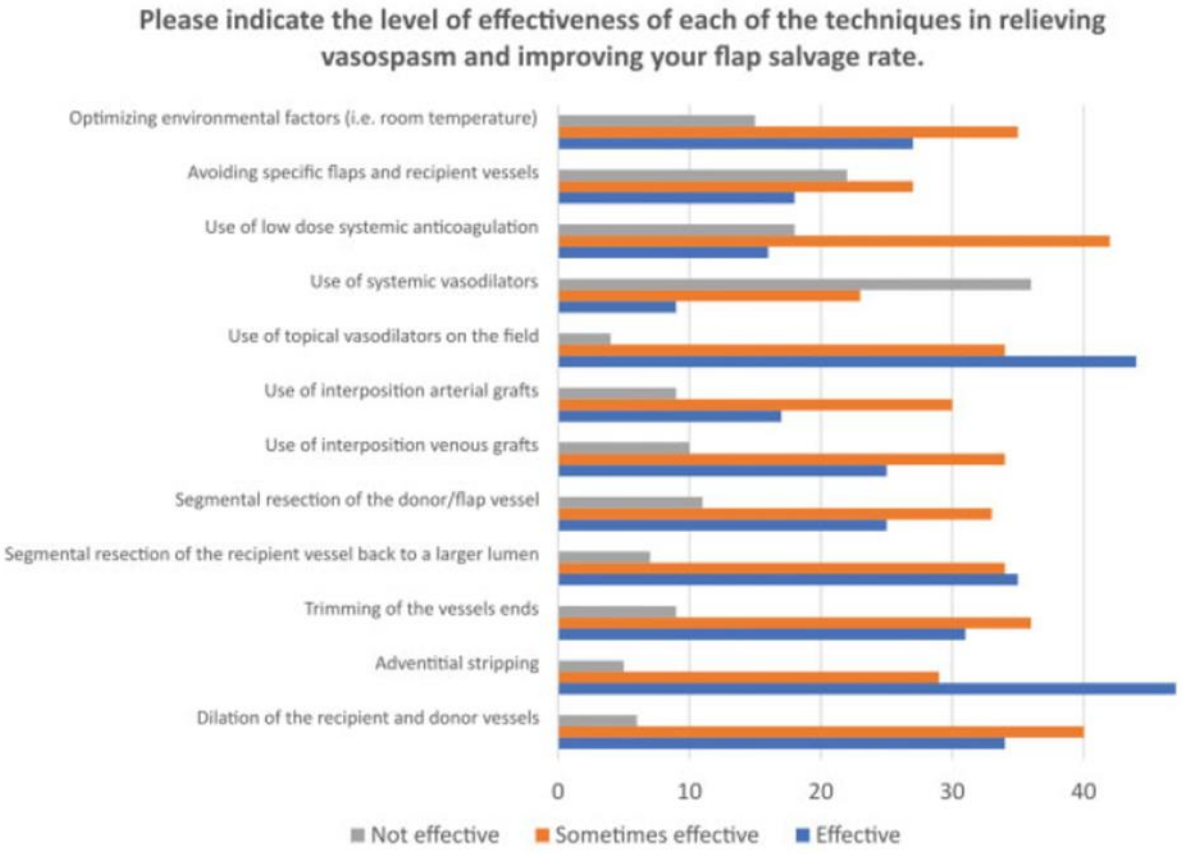

Fig. (1): Effectiveness of management techniques. [13]

There was no clear consensus on the extent of vessel resection or the methods used to determine the extent of vessel resection. Moreover, the different strategies of vessel resection were rated as having similar efficacy. In this survey, less invasive maneuvers for the management of intraoperative vasospasm were used more frequently than vessel resection. Namely, adventitial stripping and the application of topical vasodilators were the two most commonly used maneuvers and most respondents found these adjuncts to be effective. [14]

This practice is supported by the current evidence in the literature. By elevating the flap and dividing the pedicle, a local sympathectomy is performed. After flap elevation, catecholamines are liberated from degenerating adrenergic nerves, which leads to a significant rise in catecholamine concentration at the cut ends detectable at up to 2 days postoperatively. The flap enters a hyperadrenergic state for 30 hours following

elevation. Stripping the arterial adventitia aborts this phenomenon by surgically removing the nerves in the adventitial layer. [15]

However, it is important to realize that this will only affect the treated arteries, and not the rest of the flap vasculature, as shown in the setting of an ischemic hand. The perivascular tissues also appear to play a role in regulating vasospasm. When the radial artery is used as a bypass graft, maintenance of the periadventitial fat and vena comitans is one explanation as to why pedicled left internal mammary arteries have less spasm than free right internal mammary artery grafts. [16]

This strategy to transfer the radial artery as a mini free-flap (with anastomosis of the vena comitans) as opposed to a skeletonized radial artery graft has been used with success in neurosurgery bypass graft procedures. Topical pharmacological agents were used by 91% of the responding surgeons and 95% thought it was effective or "sometimes" effective. Topical vasodilators have been shown to be effective in managing microvascular vasospasm in multiple animal models as well as in humans when applied to free-flap anastomoses and internal mammary artery anastomoses in the setting of cardiac revascularization. [17]

Literature regarding the use of topical agents for postoperative vasospasm is limited to case series describing irrigation of the anastomosis with lidocaine via an angiocatheter left in place postoperatively for 48 or 72 hours. No respondents in the current survey commented on using a similar technique. A comparison study of vasodilatormedications in amurine model suggested that topical magnesium sulfate of 10%, parenteral pentoxifylline, and topical verapamil were most effective at resolving tension-induced vasospasm. [18]

However, of the respondents that did use topical vasodilators, papaverine or phosphodiesterase (PDE) inhibitors were the most popular choice (used by 83% of respondents), followed by lidocaine (used by 49% of respondents), and calcium channel blockers such as nicardipine, verapamil, and magnesium sulfate (used by 11% of respondents). At this time, high-quality comparison studies inhumans are not available, which likely explains the discordance between findings in animal models and current clinical practice. Seventy percent of participants used systemic anticoagulation, which reflects the fear of clot formation during prolonged vasospasm. [19]

Interestingly, only 23% of participants advocated the use of systemic vasodilators and very few thought it was effective. Other methods aimed at resolving vasospasm in the prolonged time frame have been described. These include papaverine mixed with fibrin and deposited at the anastomosis for delayed release, lidocaine infusion catheters maintained postoperatively to irrigate the anastomosis, nerve blocks in digit replants and revascularization, and improved pain management protocols to decrease circulating catecholamines. [20]

Unfortunately, high level evidence is lacking for any of these techniques in the microsurgical setting. The nature of the vessels also appears to have a relationship with the delayed vasospasm phenomenon. There are known differences in the structure, physiology, and spasticity of somatic (e.g., coronary), splanchnic (e.g., gastroepiploic), and limb (e.g., radial) arteries. For example, the radial artery appears to be more prone to vasospasm compared with the internal thoracic artery. [21]

Seventy-nine percent of respondents specifically mentioned the superficial inferior epigastric or lower limb vessels as being more susceptible to postoperative vasospasm. It is possible that these vessels are intrinsically more sensitive in their native state or are somehow sensitized by the transfer to the recipient site that minute vasoconstrictor stimuli such as cold, mechanical stress, or catecholamines are sufficient to cause delayed vasospasm. [22]

One hypothesis to explain this phenomenon is that the donor vessels used in microsurgery are often supplying superficial or distal tissues (e.g., SIEA and lower limb vessels) and thus aremore likely to be involved in thermoregulation and have a lower threshold for vasoconstriction comparedwith somatic and splanchnic vessels. The size of the vessels is another variable thatmust be considered —smaller vessels have a greater proclivity toward vasospasm in great toe replantation. [23]

There is no clear explanation of the physiology underlying this finding, but it does correlate to the responding surgeons noting the smaller, peripheral vessels to be more susceptible to delayed vasospasm. Size and donor

site are factors that are intrinsic to the vessel and are independent from the surgical technique and recipient site. When faced with a problematic arterial segment, A study recommend keeping these concepts in mind and encourage considering the role of resection as the definitive treatment, as it proved to be in the case report presented herein. [24]

The main limitation of this study is the survey methodology, which can be subject to significant recall bias. This can be particularly true for rare events, such as the delayed arterial vasospasm phenomenon. Due to this bias, A study also did not attempt to estimate the frequency of this phenomenon and therefore present the findings as a survey of anecdotal experiences. At this time, there are no published case series or review describing this phenomenon, and there are no databases tracking microsurgical cases with a high enough level of detail to allow analysis for the purposes of this study. [25]

The goal in conducting this investigation was to perform an initial assessment of microsurgeons' experiences with the delayed arterial vasospasm phenomenon and publish the results to bring awareness to its existence. A study designed as a survey to guide future investigations in this field, and cannot be interpreted as high-level evidence. A study hope is that awareness of this phenomenon will lead to better tracking of these occurrences so that future studies can be designed in a more rigorous fashion to provide higher level evidence. [26]

Topical Vasodilators for the Treatment

A total of 20 articles were included, representing data on 14 vasodilator agents. Drugs not amenable to local intraoperative administration or not approved for clinical use in the United States were excluded. Agents were classified into five pharmacologic categories based on their primary mechanisms: phosphodiesterase inhibitors (papaverine, pentoxifylline, and amrinone), local anesthetics (lidocaine), calcium channel blockers (nicardipine, verapamil, nifedipine, and magnesium sulfate), direct vasodilators (sodium nitroprusside, prostaglandin E1, nitroglycerin, and hydralazine), and alpha antagonists (phentolamine and chlorpromazine). A simplified summary of the mechanisms of action of topical vasodilators on vascular smooth muscle cells. [27]

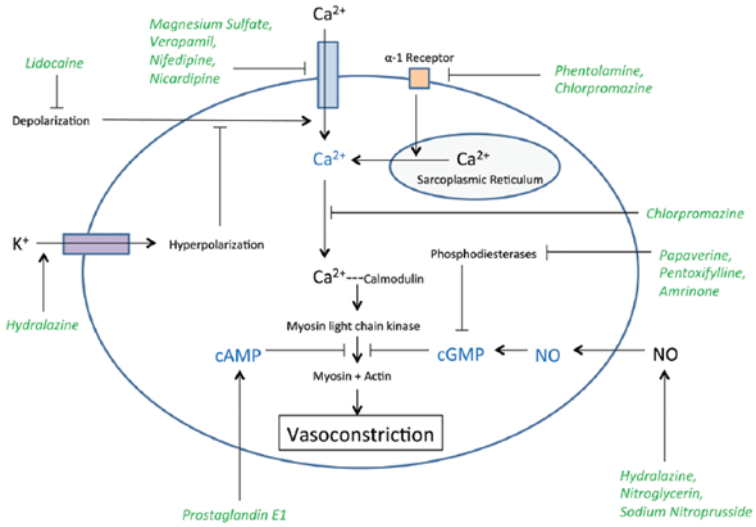

Fig. (2): Mechanisms of topical vasodilation. Simplified diagram of the mechanism of action of topical vasodilators on vascular smooth muscle cells. Vasodilators (green text) act primarily by either decreasing intracellular calcium concentrations or increasing nitric oxide, cyclic adenosine monophosphate, or cyclic guanosine monophosphate(blue text). Ca2+, calcium; cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate; NO, nitric oxide. [28]

Local Anesthetics

In addition to membrane stabilization to prevent depolarization and calcium channel activation, used topically, local anesthetics induce a direct spasmolytic effect on smooth muscle cells. [29]

Lidocaine

Primarily used for its local anesthetic and antiarrhythmic effects, the precise mechanism by which lidocaine exerts its local vasoactive properties is unclear. Vasodilation may result from inhibition of voltage-gated sodium channels, producing a decrease in intracellular sodium and calcium concentration within vascular smooth muscle cells. Others have suggested that stabilization of the cell membrane, preventing depolarization and calcium influx, is the primary mechanism of vasodilation. Still others propose that the effects are primarily mediated via endothelium-dependent effects on nearby autonomic nerve cells. [30]

In animal studies, A study found no improvement in epinephrine-induced vasospasm of the rat tail artery with application of 2% lidocaine but saw complete resolution over 15 to 30 minutes with 2% lidocaine. A study studied topical application of 2% lidocaine and 20% lidocaine in microsurgically induced vasospasm of the rabbit carotid artery and only found significant improvement with the higher dosage. A study also reported 2% lidocaine to be effective in a blood-induced spasm model using the rat hindlimb. A study found significant improvement in epinephrine-induced vasospasm of the rat femoral artery after application of 10% lidocaine. [31]

The ideal concentration of lidocaine to resolve microvascular vasoconstriction has been reported to be 12% because this dose was as effective as, but less toxic than, 2% lidocaine in a rat tail artery study that evaluated ergotamine-induced vasospasm. In a similar follow-up study, the same group found 12% lidocaine to have a greater effect than lower concentrations, with minimum local tissue toxicity. A study used a rat femoral artery model in which foreign blood was used to induce vasospasm, and topically applied lidocaine at concentrations from 2% to 40%. [32]

The duration of the effect increased with increasing concentrations, although the spasmolytic effect was unchanged. These authors suggested that 2% lidocaine was most effective for use as a topical agent during micro surgery. The same finding had also been suggested in another rat model that compared 2% and 1% lidocaine. For humans, the safety of doses in excess of 2% has not been conclusively established; however, A study reported no evidence of systemic toxicity in a four patients series after topical administration of 2% lidocaine during microvascular reconstruction cases in which peripheral lidocaine concentrations peaked at 1.5 μg/ml, well below the established toxicity level of 5 to 10 μg/ml. At low concentrations, lidocaine has been reported to potentiate vessel constriction. [33]

A study reported that 2% lidocaine actually worsened vessel spasm in a rat cremaster muscle model, with an additional significant increase in vessel diameter at 5 and 10 minutes. As a result of these concerns, a number of studies have called into question the utility of clinical use of this concentration as a topical agent. Other studies have found lower concentrations of lidocaine to be effective. [34]

In an in vivo study of the effect of 2% lidocaine on rat femoral arteries in which vasospasm was not chemically induced, Kerschner and Futran found a significantly increased vessel diameter relative to control. A study used 2% topical lidocaine in treatment of epinephrine-induced vasospasm of rat femoral arteries and found an immediate, significant increase in flow. [35]

When 2% lidocaine was applied without prior epinephrine, there was an initial decrease in flow at 1 minute, followed by a significant increase at 2 minutes, and peak flow rate at 9 minutes, with a total duration of at least 15 minutes. Overall, lidocaine is likely a dose-dependent agent, with controversy regarding its practical use to relieve vasospasm. Although higher concentrations may be effective experimentally, the potential for local and systemic complications limits its clinical implementation. [36]

Magnesium Sulfate

Commonly used for electrolyte repletion and treatment of eclampsia and torsades de pointes, magnesium sulfate also has bronchodilatory and vasodilatory properties possibly related to calcium channel inhibition. Huang and Li found no significant effect on rat cremaster vessel diameter when magnesium sulfate was applied after epinephrine- induced vasoconstriction. [37]

However, in a recent study of traction-induced vasospasm in a rat hindlimb model, A study found topical application of 10% magnesium sulfate to be the most reliable agent (from a field of 11) in both reduction of

vasospasm and time to hyperperfusion, although results with regard to rapidity and duration of effect with topical application were lacking. Because of a favorable overall pharmacologic profile with systemic administration, use of magnesium sulfate interoperatively certainly merits further investigation. [38]

VASOSPASM OF THE FLAP PEDICLE – MAGNESIUM SULPHATE RELIEVES VASOSPASM

Vasospasm is a common problem in microvascular surgery. It is a localized contraction of the vascular smooth muscle in contrast to a generalized vasoconstriction, which is caused by influences of central nervous system. Vasospasm usually develops as a result of surgical manipulation of small vessels of the vascular pedicle during free flap elevation. [39]

Often, it causes only temporary and incomplete obstruction of the vessels. In some cases, however, a prolonged vasospasm may result in formation of a thrombus and cause a complete obstruction of the vessel. Definition of vasospasm, its pathogenesis and clinical consequences is mentioned in the first part of vasospasm study, which is published as a separate article (Vasospasm of the Flap Pedicle: The New Experimental Model on Rat). [40]

Surgical treatment of acute vasospasm is rarely effective, therefore pharmacologic therapy should be administered The ideal chemical agent is still being sought. The effects of different vasodilating drugs were compared in the second part of study, which is also published as a separate article (Akhondi & Sarkoohi, 2023). Vasospasm was provoked by tension applied on the pedicle of a groin flap on rat, magnesium sulphate was the most efficient chemical agent among a number of studied drugs. According to knowledge, the effect of magnesium on the pedicle of the flap in porcine model has not been studied yet. [41].

Correlation

Several studies were dedicated to an investigation of the vasospasm on a porcine model. A study used new experimental model that was influenced by previous studies on a rodent model (Vasospasm of the Flap Pedicle – The New Experimental Model on Rat). A study new experimental model was based on the axial pattern free flap. The vasospasm was repeatedly induced using exactly defined axial tension that was applied on the flap pedicle. [42]

The weight of the weight, that consistently and safely produced vasospasm, was determined on two pigs operated before this study by gradually adding the weights on the pulling thread. The weight of 160g consistently stimulated vasospasm in all subjects and vasospasm lasted long enough to allow the tested drug to show its effect. By removing adventitia in some extent, the tissue wrapped around vessels was insignificant and the force was applied straight on the vessel wall. Also, magnesium infiltrated the vascular wall easier. [43]

Automated detection of the time values on the signal curves ensured maximum objectivity and accuracy in obtaining measured values. The pathogenesis of vasospasm resulting from pulling the pedicle is still not clear. One of the possible explanations is direct myogenic response of the smooth vascular wall muscle. Stretching arterial smooth muscle to 1.2 times of its resting length results in maximal phosphorylation of myosin light chains and smooth muscle contraction. [44]

Although the vasodilator properties of magnesium ions were well documented both in vitro and in vivo, the exact mode of action of this drug on vasospasm is still not fully understood. The best explaining theory of mechanism of action is likely to be related to competitive inhibition between magnesium and calcium ions for binding sites on the myosin light chain kinase regulatory protein, Calmodulin. [45]

Data obtained from this study of different calcium channels (verapamil, nimodipine, nitredipine and nisoldipine) point at considerable heterogeneity of its active sites. Magnesium sulphate probably acted in all types of calcium channels of the vessels in different organs. Conversely, effect of calcium channels blockers is strongly organ dependent. In vitro, A study studied effect of magnesium on the vascular ring segments from human coronary arteries obtained by autopsy within 5 hours. Magnesium significantly inhibited the tonic contraction at concentrations of 1mM and 2mM, but increased the amplitude of periodic contraction. [46]

A study found that intravenous magnesium sulphate dilated the spastic basilar artery (provoked by the blood in the subarachnoid space) in the rat from 50% of the baseline diameter to 75% and topical application of magnesium sulphate dilated the spastic basilar artery to 150% of the baseline diameter. In clinical studies, A

study proved positive effect on relieving cerebral vasospasm when plasma concentration was maintained at 1–1.5 mmol/l and magnesium was also efficient when the concentration was twice higher. [47]

A study confirmed these findings on cerebral vasospasm in pilot prospective randomized controlled studies. Magnesium therapy may be more effective if magnesium is administered as a preventive measure to protect against vasospasm rather than to treat a completely developed vasospasm. A study have been using perivascular (intra-adventitial) injection of magnesium sulphate empirically in microsurgical procedures from the 1990s – its effectiveness appears to be reliable despite the fact that no evidence has been provided yet. [48]

Magnesium sulphate is a readily available, inexpensive substance that proved its efficacy in several experimental and clinical studies. This study confirmed findings based on experimental study on a rodent model as well as clinical observations. According to knowledge, this is the first report that proved magnesium efficacy on relieving mechanically produced vasospasm of the flap pedicle on a porcine model. [49]

In brief, Magnesium sulphate shortened significantly the mechanically provoked vasospasm on superficial inferior epigastric flap in a porcine model. Further clinical studies are needed to prove the effect in humans. [47]

Prevention of Vasospasm by Topical Application of Lidocaine

Free-tissue transfer with anastomosis has become an important microsurgical technique in plastic and reconstructive surgery. This technique is used when the bones or tendons are exposed, sensory restoration is required during injury to the extremities, and also in head and neck surgeries. [50]

In such cases, it is difficult to obtain sufficient blood flow to the anastomosis. The lack of blood flow from the recipient artery adversely affects the results of the free-tissue transfer. Moreover, the occurrence of vasospasm and thrombosis after an anastomosis is created by harvesting the recipient arteries around the scar can cause necrosis during tissue transfer. [51]

In clinical surgery, lidocaine is topically applied on the anastomotic region to prevent and treat vasospasm. Various studies in anesthesiology have assessed the effect of lidocaine application in general, the topical application of a high concentration of lidocaine is thought to be more effective in improving blood flow and treating vasospasm. However, an excess amount of lidocaine can cause side effects involving cardiac circulation or the central nervous system. Therefore, the quantity of lidocaine used must be carefully monitored, even in case of its topical application. [52]

Correlation

Thrombosis is a major problem during free-tissue transfer. A study reported that of 493 cases of free-tissue transfer with anastomosis, thrombectomies were required in 10% cases, of which 69% were successful, and the overall success rate was 96%. Although the success rate of free-tissue transfers with anastomosis has recently increased, A study sometimes observe the disruption of the blood flow after the anastomosis is closed because of the degeneration of vessels or the thrombosis by vasospasm. [53]

Therefore, maintaining sufficient blood flow and preventing and treating vasospasm can decrease the incidence of thrombosis and increase the success rate of free-tissue transfers. In particular, in free-tissue transfer surgeries, vasospasm after anastomosis closure is a major complication, leading to thrombosis in the anastomotic region or the failure of distal circulation to the flap because of the decreased blood flow. A study reported that vasospasm after an injury is caused by changes in the smooth muscle cells of a blood vessel: decrease in vasodilator levels, alterations in receptors/nerves/cell membrane, or a functional disorder. [54]

Therefore, Lidocaine is generally administered as a local anesthetic and topically applied to treat vasospasm after microsurgery. There are many kinds of local anesthetics, and most microsurgeons use lidocaine for treating vasospasm because it acts fast and is simple to use. Lidocaine is believed to effect a change in the ion influx to the membranes of nerve cells and smooth muscles; therefore, it is effective in treating vasospasm. [55]

In general, a higher concentration of lidocaine is more effective in treating vasospasm. A study reported that a concentration of 2% lidocaine is most effective for treating vasospasm. However, A study reported that although 2%, 16%, and 12% lidocaine affected the vasodilator level and increased blood flow, 2% lidocaine

caused significant edema and infirmity of the vessel tissue; therefore, A study concluded that 12% lidocaine is the most effective. A study also studied the amount of lidocaine that must be topically applied for increasing the blood flow and treating vasospasm. [56]

The maximum single dose of lidocaine that can be given as a local anesthetic is 15 mg/kg. A blood lidocaine concentration exceeding 5 to 10 g/mL has severe adverse effects on the central nervous system (eg, turbulence, excitement, and convulsions, etc) or the cardiac and respiratory systems (changes in heartbeat, blood pressure, and A-V conduction; breathing difficulties). A study reported that the administration of an excessive amount of lidocaine can increase the heartbeat, blood pressure, or result in uneasy behavior in volunteers. [57]

Further, A study aimed to examine whether a small quantity of lidocaine had sufficient effects. A study used 0.2 mL of 2% lidocaine because in A study experience, this dose has proven to be sufficient if the vessel diameter is 0.6 to 1.2 mm and if the distance between the catheter tip for topical application and the anastomotic region is 5 to 10 mm during clinical surgery. A study decided on 1.0 mL/h of lidocaine on the basis of Ichioka's report and A study result that a single dose of 0.2 mL had the effect from 10 minutes to 12 minutes. [58]

In contrast, when 1.0 mL/h of 2% lidocaine was continuously applied, the blood flow slowly increased to 3 times the preapplication levels and reached a plateau 10 minutes after the start of application. Therefore, A study conclude that to generate rat models of vasospasm, epinephrine should be applied 10 minutes after the start of continuous application of lidocaine. Although the average blood flow during continuous application was higher than that in the control group, the difference was significant only at 3 minutes to 4 minutes after the start of application. Therefore, A study think that 2% was an insufficient concentration for continuous application. [59]

However, the increase in blood flow was statistically significant at 1 minute to 13 minutes after lidocaine application. A study also aimed to understand how the continuous topical application of 2% lidocaine could improve the vessel contraction induced by epinephrine. After the administration of lidocaine, some time would be required for the effect to show. [60]

In case of continuous application of lidocaine, the blood flow briefly decreased after the application of epinephrine but improved after 4 minutes and returned to the level before application at 9 minutes. Moreover, the flow remained at 110% of the original flow after 11 minutes. Mann-Whitney U test showed that there was a statistically significant difference in the blood flow after 15 minutes. This result reveals that although the maximum blood flow after the topical application of 1.0 mL/h of 2% lidocaine was lower than that after a single application of 0.2 mL, continuous application definitely had a preventive effect on vasospasm. [61]

A study therefore believe that persistent vasospasm should first be treated with several topical applications of lidocaine; if this helps improve the condition, continuous topical application can be subsequently used as a preventive measure. Examination for a longer time is particularly relevant in case of continuous topical application because lidocaine is expected to deposit around the vessel. This study can then allow us to determine if a drainage tube needs to be placed around the vessel during clinical surgery, to prevent the deposition of lidocaine. [62]

In brief, the changes in blood flow in the femoral artery of rats after single and continuous topical application of 2% lidocaine. Further, A study generated rat models of vasospasm by using epinephrine and then examined the preventive effect on vasospasm by using the above 2 methods. A study results suggest that although the effect lasts for a short period, a single application of 2% lidocaine has a rapid effect and is effective for treating a sudden manifestation of vasospasm. [63]

In contrast, continuous topical application may be more effective for maintaining the blood flow and preventing vasospasm. As they are insistently inference by animal study, one should be careful in applying lidocaine in clinical surgery. In particular, to determine the safety and obtain good results, it is important to monitor the blood concentration of lidocaine during continuous infusion and confirm whether the amount infused per hour is safe. [52]

References

1. Sutaria, AH, Masood, S, Saleh, HM, & Schlessinger, J. (2023). Acne vulgaris. In StatPearls [Internet]. StatPearls Publishing.
2. Firlej, E, Kowalska, W, Szymaszek, K, Roliński, J, & Bartosińska, J. (2022). The Role of Skin Immune System in Acne. Journal of Clinical Medicine, 11(6), 1579. https://doi.org/10.3390/jcm11061579
3. Kutlu, Ö, Karadağ, AS, & Wollina, U. (2023). Adult acne versus adolescent acne: a narrative review with a focus on epidemiology to treatment. Anais Brasileiros de Dermatologia, 98(1), 75–83. https://doi.org/10.1016/j.abd.2022.01.006
4. Powers, C, Huynh, T, & Badon, H. (2022). Dermatologic differences in a diverse population.
5. Teder-Laving, M, Kals, M, Reigo, A, Ehin, R, Objärtel, T, Vaht, M, ... & Kingo, K. (2023). Genome-wide meta-analysis identifies novel loci conferring risk of acne vulgaris. European Journal of Human Genetics, 1-8.
6. Umborowati, MA, Ollyvia, ZZ, & Febriana, N. (2022). THE IMPACT OF ACNE VULGARIS ON THE QUALITY OF LIFE IN TEEN PATIENTS. Periodic Epidemiology Journal/Jurnal Berkala Epidemiologi, 10(2).
7. Yıldırım, F, Mert, B, Çağatay, EY, & Aksoy, B. (2022). Predictors of quality of life in adults and adolescents with acne: A cross-sectional study. Indian Journal of Dermatology, 67(3), 239.
8. Şahin, GÖ, Özer, TT, & Durmaz, S. (2023). Investigation of fungus at stratum corneum of patients with acne vulgaris. Microbial Pathogenesis, 175, 105982.
9. Escamilla-Cruz, M, Magaña, M, Escandón-Perez, S, & Bello-Chavolla, OY. (2023). Use of 5-Alpha Reductase Inhibitors in Dermatology: A Narrative Review. Dermatology and Therapy, 13(8), 1721-1731.
10. Jin, Z, Song, Y, & He, L. (2023). A review of skin immune processes in acne. Frontiers in Immunology, 14, 1324930.
11. Nakase, K, Momose, M, Yukawa, T, & Nakaminami, H. (2022). Development of skin sebum medium and inhibition of lipase activity in Cutibacterium acnes by oleic acid. Access microbiology, 4(10), acmi000397. https://doi.org/10.1099/acmi.0.000397
12. Xu, Y, & Qiao, J. (2022). Association of insulin resistance and elevated androgen levels with Polycystic Ovarian Syndrome (PCOS): a review of literature. Journal of Healthcare Engineering, 2022.
13. Bosanac, I., Šegota, S., & Šimić, I. (2018). The role of sex hormones in acne vulgaris. Clinical, Cosmetic and Investigational Dermatology, 11, 15–23.
14. Ilyas, M., Khan, SA, & Siddiqui, MA. (2020). Corticotrophin-releasing hormone and stress: a review. Reviews in Endocrine & Metabolic Disorders, 21(2), 127-136.
15. Cong, W, Wang, X, Liu, Z, Li, H, & Liu, Z. (2019). Melanin modulates inflammatory cytokine production and the expression of TLR2 and TLR4 in human keratinocytes. International Journal of Molecular Sciences, 20(15), 3706.
16. Zhu, W, Wang, HL, Bu, XL, Zhang, JB, & Lu, YG. (2022). A narrative review of research progress on the role of NLRP3 inflammasome in acne vulgaris. Annals of Translational Medicine, 10(11).
17. Huang, Y, Liu, L, Hao, Z, Chen, L, Yang, Q, Xiong, X, & Deng, Y. (2022). Potential roles of gut microbial tryptophan metabolites in the complex pathogenesis of acne vulgaris. Frontiers in Microbiology, 13, 834472.
18. Spittaels, KJ, Van Uytfanghe, K, Zouboulis, CC, Stove, C, Crabbé, A, & Coenye, T. (2021). Porphyrins produced by acneic Cutibacterium acnes strains activate the inflammasome by inducing K+ leakage. IScience, 24(6), 102575.
19. Dagnelie, M, Corvec, S, Timon-David, E, Khammari, A, & Dréno, B. (2022). Cutibacterium acnes and Staphylococcus epidermidis: The unmissable modulators of skin inflammatory response. Experimental Dermatology, 31(3), 406–412.
20. Sánchez-Pellicer, P, Navarro-Moratalla, L, Núñez-Delegido, E, Ruzafa-Costas, B, Agüera-Santos, J, & Navarro-López, V. (2022). Acne, Microbiome, and Probiotics: The Gut–Skin Axis. Microorganisms, 10(7), 1303.
21. Zhang, H, & Zhang, Z. (2023). Genetic Variants Associated with Acne Vulgaris. International Journal of General Medicine, 3843-3856.
22. Zúñiga-Gazcón, H, Delgado, MAF, Mayorga, DES, Macias, CC, & Ramírez, MAA. (2022). Association of Genetic Factors in the Occurrence of Acne Vulgaris and its Implication in the Development of Severe Acne. International Journal Of Medical Science And Clinical Research Studies, 2(10), 1094–1098.
23. Piquero-Casals, J, Morgado-Carrasco, D, Rozas-Muñoz, E, Mir-Bonafé, JF, Trullàs, C, Jourdan, E, ... & Krutmann, J. (2023). Sun exposure, a relevant exposome factor in acne patients and how photoprotection can improve outcomes. Journal of Cosmetic Dermatology.
24. Austin, D, Adepoju, OO, & Duru, N. (2021). A practical approach to acne and post-inflammatory hyperpigmentation in skin of color. Journal of the American Academy of Dermatology.
25. Markovic, M, Soldatovic, I, Bjekic, M, & Sipetic-Grujicic, S. (2020). Adolescents' self perceived acne-related beliefs: from myth to science. Anais Brasileiros de Dermatologia, 94, 684–690.
26. Prieux, R, Ferrara, F, Cervellati, F, Guiotto, A, Benedusi, M, & Valacchi, G. (2022). Inflammasome involvement in CS-induced damage in HaCaT keratinocytes. In Vitro Cellular & Developmental Biology-Animal, 58(4), 335– 348.
27. Khan, A, & Chang, MW. (2022). The role of nutrition in acne vulgaris and hidradenitis suppurativa. Clinics in Dermatology, 40(2), 114-121.

28. Barrea, L, Di Pietro, C, De Santis, A, Zunino, F, Aragona, G, Montalbano, G, et al. (2021). Prevalence and risk factors of acne in young adults: a cross-sectional observational study. The Journal of Clinical and Aesthetic Dermatology, 14(7), 33-42.
29. Ah-Thiane, NS, Diallo, I, Pouye, K, Dia, S, Fall, A, Guèye, M, et al. (2022). Prevalence of acne vulgaris in Dakar, Senegal, and its association with nutritional factors. International Journal of Dermatology, 61(2), 185-190.
30. Baldwin, H, & Tan, J. (2021). Effects of diet on acne and its response to treatment. American Journal of Clinical Dermatology, 22, 55–65.
31. Seetan, K, Kiwan, B, Kasasbeh, D, Ayesh, M, Al-zoubi, O, Al-sarhan, B, & Al-majali, H. (2023). Impact of Lifestyle Factors on the development and severity of Acne Vulgaris: a cross sectional study.
32. Sachdeva, M, Tan, J, Lim, J, Kim, M, Nadeem, I, & Bismil, R. (2021). The prevalence, risk factors, and psychosocial impacts of acne vulgaris in medical students: A literature review. International Journal of Dermatology, 60(7), 792–798.
33. Tefft, KR, Balboul, S, Safai, B, Cline, A, & Marmon, S. (2022). Diagnosis of stress-associated dermatologic conditions in New York City safety-net hospitals during the COVID-19 pandemic. Journal of the American Academy of Dermatology, 87(5), e177–e179.
34. Xerfan, A, El Ghalbzouri, A, & Zouboulis, CC. (2021). Sleep deprivation in acne vulgaris: a new perspective on a common skin disease. Journal of the European Academy of Dermatology and Venereology.
35. Hudson, BN, Jacobs, HR, Philbrick, A, Zhou, XA, Simonsen, MM, Safirstein, JA, & Rotolo, SM. (2022). Drug-induced acne with elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis. Journal of Cystic Fibrosis, 21(6), 1066-1069.
36. Piquero-Casals, J, Morgado-Carrasco, D, Rozas-Muñoz, E, Mir-Bonafé, JF, Trullàs, C, Jourdan, E, ... & Krutmann, J. (2023). Sun exposure, a relevant exposome factor in acne patients and how photoprotection can improve outcomes. Journal of Cosmetic Dermatology.
37. Araviiskaia, E, Layton, AM, Estebaranz, JLL, Ochsendorf, F, & Micali, G. (2022). The synergy between pharmacological regimens and dermocosmetics and its impact on adherence in acne treatment. Dermatology Research and Practice, 2022.
38. Rosso, J. (2022). SUPPLEMENT INDIVIDUAL ARTICLE: Optimizing Skin Care in Acne Treatment-Evaluation of a Designated Cleanser and Moisturizer Regimen With Improvement in Clinical Outcomes. Journal of Drugs in Dermatology: JDD, 21(12), SF3509935–SF35099314.
39. Goh, C, Wu, Y, Welsh, B, Abad-Casintahan, MF, Tseng, C, Sharad, J, Jung, S, Rojanamatin, J, Sitohang, IBS, & Chan, HNK. (2023). Expert consensus on holistic skin care routine: Focus on acne, rosacea, atopic dermatitis, and sensitive skin syndrome. Journal of Cosmetic Dermatology, 22(1), 45–54.
40. Puaratanaarunkon, T, & Asawanonda, P. (2022). A randomized, double blinded, split-face study of the efficacy of using a broad spectrum sunscreen with anti- inflammatory agent to reduce post inflammatory hyperpigmentation after picosecond laser. Clinical, Cosmetic and Investigational Dermatology, 331– 337.
41. Chilicka, K, Rusztowicz, M, Szyguła, R, & Nowicka, D. (2022). Methods for the improvement of acne scars used in dermatology and cosmetology: a review. Journal of Clinical Medicine, 11(10), 2744.
42. Liu, L, Xue, Y, Chen, Y, Chen, T, Zhong, J, Shao, X, & Chen, J. (2023). Prevalence and risk factors of acne scars in patients with acne vulgaris. Skin Research and Technology, 29(6), e13386.
43. Xu, W, Sinaki, DG, Tang, Y, Chen, Y, Zhang, Y, & Zhang, Z. (2024). Acne-induced pathological scars: pathophysiology and current treatments. Burns & Trauma, 12, tkad060.
44. Zhou, C, Vempati, A, Tam, C, Khong, J, Vasilev, R, Tam, K, ... & Hazany, S. (2023). Beyond the surface: A deeper look at the psychosocial impacts of acne scarring. Clinical, Cosmetic and Investigational Dermatology, 731-738.
45. Amer, AMM, Zakzouk, AMA, & Samir, M. (2023). Options of Treatment of Post Acne Scar. The Egyptian Journal of Hospital Medicine, 91(1), 4434-4439.
46. Rusciani, A, Ricci, F, & Curinga, G. (2023). Acne scar treatment. In European Handbook of Dermatological Treatments (pp. 1135-1141). Cham: Springer International Publishing
47. Lee, JD, & Oh, MJM. (2023). Atrophic Acne Scar and Histology. In Lasers in Dermatology: Parameters and Choice: With Special Reference to the Asian Population (pp. 173-180). Singapore: Springer Nature Singapore.
48. Bhargava, N, Khandelwal, N, & Bhatnagar, A. (2018). Acne scarring: A comprehensive review. The Indian Journal of Dermatology, 63(4), 369.
49. Rimon, A, Rakov, C, Lerer, V, Sheffer-Levi, S, Oren, SA, Shlomov, T, ... & Hazan, R. (2023). Topical phage therapy in a mouse model of Cutibacterium acnes-induced acne-like lesions. Nature Communications, 14(1), 1005.
50. Amuzescu, I, Buteanu, C, Constantin, M, & Rusu, E. (2024). An Update on Acne Vulgaris Treatment. Current Opinion in Endocrinology, Diabetes and Obesity, 31(2), 128-133.
51. Mavranezouli, I, Daly, CH, Welton, NJ, Deshpande, S, Berg, L, Bromham, N, ... & Healy, E. (2022). A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. British Journal of Dermatology, 187(5), 639-649.

52. Sadati, MS, Yazdanpanah, N, Shahriarirad, R, Javaheri, R, & Parvizi, MM. (2023). Efficacy of metformin vs. doxycycline in treating acne vulgaris: an assessor-blinded, add-on, randomized, controlled clinical trial. Journal of Cosmetic Dermatology.
53. Daly, AU, Baptista Gonçalves, R, Lau, E, Bowers, J, Hussaini, N, Charalambides, M, ... & Layton, AM. (2023). A systematic review of isotretinoin dosing in acne vulgaris. JEADV Clinical Practice, 2(3), 432-449.
54. Reynolds, RV, Yeung, H, Cheng, CE, Cook-Bolden, F, Desai, SR, Druby, K, ... & Barbieri, JS. (2024). Guidelines of care for the management of acne vulgaris. Journal of the American Academy of Dermatology.
55. Attia, E. (2024). Atrophic Postacne Scar Treatment: Narrative Review. JMIR dermatology, 7, e49954.