Vasospasm of the Flap Pedicle: The Effect of 11 of the Most Often Used Vasodilating Drugs. Comparative Study in a Rat Model

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Background: There has been no review study published yet comparing the effects of the vasodilating drugs that are most often used in clinical practice empirically. The aim of the authors' study was to perform this comparison and to select the drugs that are able to release vasospasm and the drugs that reduce vasospasm duration most effectively in an experimental model in vivo.
Methods: Pedicled groin flaps were dissected in 300 male Wistar rats. Vasospasm was induced by tension applied on the pedicle in the axial direction using a 15-g weight. The blood perfusion of the flap was monitored using a laser Doppler device. The duration of vasospasm was defined as the time from the release of tension until blood flow began to rise. These times were detected using automated computerized detection. The effects of 11 different drugs were studied in 14 groups. The drugs were applied locally; some of them were tested in different concentrations or applied parenterally.
Results: Ten percent magnesium sulfate reduced the duration of vasospasm most effectively ($p < 0.01$). Verapamil applied locally and also pentoxifylline applied parenterally were also very effective. In contrast, the duration of vasospasm was extended after local application of 2% lidocaine ($p < 0.01$).
Conclusions: The authors concluded that 10% magnesium sulfate applied locally has the best ability to relieve surgically induced vasospasm because of the highest level of significance and reliability. The finding that local application of 2% lidocaine prolongs vasospasm may be surprising. (*Plast. Reconstr. Surg.* 134: 574e, 2014.)

Microsurgical free tissue transfer is currently an important method in reconstructive surgery, and vasospasm is a common complication associated with flap dissection. Vasospasm is a local and persistent spastic contraction of smooth muscles in the vessels that is caused by pathologic stimulus. Vasospasm is a functional problem that usually resolves spontaneously. In case vasospasm is prolonged, the blood supply of tissues is significantly reduced and flap failure may occur.[1–6] The pathogenesis of vasospasm is complex, and it is often associated with other pathologic entities, such as the mechanism of thrombosis, ischemia-reperfusion injury of the flap, or the no-reflow phenomenon.[7–12] Thus, pharmacologic interventions for vascular complications in microsurgery may focus on thrombosis (antiaggregants and anticoagulants), ischemia-reperfusion injury or the no-reflow phenomenon (drugs that modulate flap tolerance to ischemia), and vasospasm. We believe that no study comparing the effects of the most often used vasodilating drugs on mechanically induced vasospasm of the flap pedicle has been published yet.

The main objective of our previous experiments was to develop an experimental model that would simulate reliably possible surgical causes of vasospasm induction during flap dissection. This model should also enable easy and standardized application of the drug while being well adapted for testing the drug within the study.[13]

The main aim of this study was (1) to compare the effects of different vasodilating drugs with the control group and also to compare their effect

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Table 1. Medications Used in the Experiment

Group	Drug Name	Name of Active Substance	Route of Administration	Manufacturer	Median t_v (sec)	Median t_{hp} (sec)
1	Agapurin injection	Pentoxifyllinum, 20 mg/ml	Parenteral	Zentiva a.s., Hlohovec, Slovak Republic	138	936.67
2	Agapurin injection	Pentoxifyllinum, 20 mg/ml	Local	Zentiva a.s., Hlohovec, Slovak Republic	90	298
3	Prostavasin injection	Alprostadilum, 4 μg/ml	Parenteral	Schwarz Pharma AG, Monheim, Germany	183	1161
4	Perlinganit	Glyceroli trinitras, 1 mg/ml	Local	Schwarz Pharma AG, Monheim, Germany	261	773
5	Lidocaine 2%	Lidocaini hydrochloridum, 20 mg/ml	Local	Egis Pharmaceuticals PLC, Budapest, Hungary	1184	2217
6	Magnesium sulfuricum 10%	Magnesii sulfas heptahydricus, 0.1 g/ml	Parenteral	Hoechst-Biotika s.r.o., Martin, Slovak Republic	158	577
7	Magnesium sulfuricum 10%	Magnesii sulfas heptahydricus, 0.1 g/ml	Local	Hoechst-Biotika s.r.o., Martin, Slovak Republic	119	315
8	Magnesium sulfuricum 20%	Magnesii sulfas heptahydricus, 0.2 g/ml	Local	Hoechst-Biotika s.r.o., Martin, Slovak Republic	180	617
9	Marcaine 0.5%	Bupivacaini hydrochloridum, 5 mg/ml	Local	AstraZeneca, UK, Ltd., Macclesfield, Cheshire, United Kingdom	209	1105
10	Mesocaine 1%	Trimecaini hydrochloridum, 10 mg/ml	Local	Zentiva a.s., Praha, Czech Republic	174	701
11	Nipruss	Sodium nitroprusside, 1 mg/ml	Local	Schwarz Pharma AG, Monheim, Germany	205	602
12	Papaverin Spofa injection	Papaverini hydrochloridum, 30 mg/ml	Local	VUAB Pharma a.s., Roztoky, Czech Republic	187	433
13	Lekoptin injection	Verapamili hydrochloridum, 2.5 mg/ml	Local	Lek Pharmaceuticals d.d., Ljubljana, Slovenia	44	275
14	Prostavasin injection	Alprostadilum, 4 μg/ml	Local	Schwarz Pharma AG, Monheim, Germany	251	900
15	Control group				379	883

t_v, vasospasm duration; t_{hp}, time to hyperperfusion.

between the groups, (2) to select the drugs that are able to reduce vasospasm duration, and (3) to select the drugs that reduce vasospasm duration most effectively. Our hypothesis was that application of the studied drugs will reduce the duration of mechanically induced vasospasm in the experimental model.

MATERIAL AND METHODS

Three hundred male Wistar rats were used. The median weight of the rats was 358.2 ± 51.5 g. The experiment was approved by the Ethics Committee at St. Anne University hospital in Brno and performed under standard conditions (i.e., temperature, 24° to 25°C; light conditions; sterility). The rats were anesthetized using ketamine (100 mg/kg) and xylazine (10 mg/kg). Ether was used at the beginning of anesthesia. All dissections were performed by the same surgeon. The effects of 11 different drugs were studied in 14 groups. The drugs were mostly applied locally, and the effects of the most potent drugs were tested also in different concentrations or applied parenterally/intraperitoneally (Table 1). No drug was applied in the control group.

Dissection Technique

The holder for the laser Doppler probe (small straight probe 407-1; PeriMed AB, Järfälla, Sweden) was placed on the skin at a defined point (2 cm above and laterally from the genital tubercle). A skin paddle of 1.5 × 1.5 cm of the groin flap based on the superficial inferior epigastric artery was outlined. The flap pedicle was designed at the medial part of the flap. The pedicle was dissected sharply, leaving a thick fat and connective tissue layer surrounding the pedicle (Fig. 1). Two strips of perivascular connective tissue ("perivascular flaps") with a length of 0.5 cm that remained distally connected with the pedicle were raised (Fig. 2). One of them comprised the inferior epigastric nerve. A weight of 15 g was attached to the above-described perivascular flaps by the atraumatic monofilament nylon suture (Premilene 6-0; B. Braun Melsungen AG, Melsungen, Germany). All dissections were performed by the same surgeon, as in the control group.

Timing of the Experiment, Induction of Vasospasm, and Application of Drugs

After dissection, the rat was moved to the measuring area and the flap was left resting for

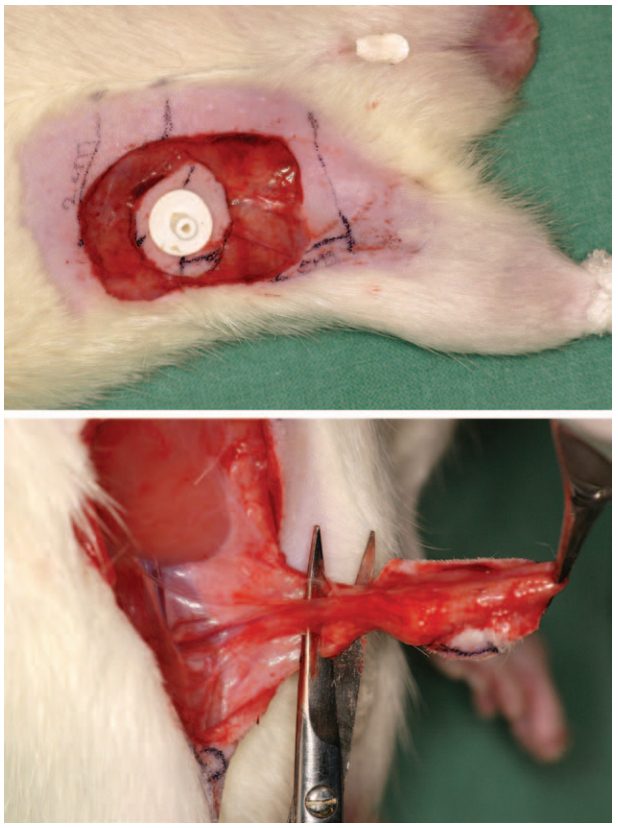

Fig. 1. Flap dissection. The flap was dissected out sharply. The pedicle was neither touched by instruments nor pulled or traumatized in any other way, to prevent induction of vasospasm.

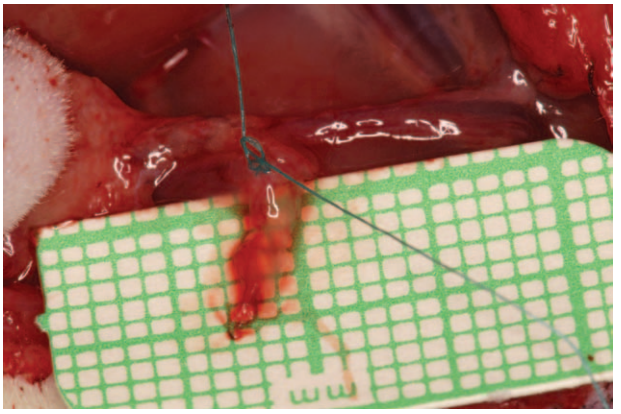

Fig. 2. Pedicle dissection. Two perivascular flaps (stripes) were created on both sides of the pedicle using sharp dissection by scissors.

25 minutes. Then, the laser Doppler probe was attached to the holder, the recording of flap perfusion was turned on, and the flap was left for another 5 minutes resting. Next, the preprogrammed script was begun; the basal level of the flap perfusion was measured for 5 minutes. The 15-g weight was gently hung on the block and the pedicle was pulled for the next 5 minutes and then released. Administration of drugs began immediately after application of the weight. The drugs were applied locally by continuous manual application of drops on the flap pedicle; the rate was 0.5 ml/minute, and dropping continued for 2 minutes after releasing the weight or the drugs were administered systemically using a 2-ml bolus of drug solution given intraperitoneally. Following the stimulus, the perfusion curve was recorded for 30 minutes. The time of stimulation termination was set as 0 (Table 2). Each step of the experiment was defined by the appropriate time period using PeriSoft for Windows software script (PeriSoft for Windows 2.5; PeriMed) and an appropriate voice signal allowed us to control the timing of the experiment.

Laser Doppler Perfusion Measurements

A laser Doppler flowmeter (PeriFlux system 5000; PeriFlux 5010 Laser Doppler Perfusion Monitor unit, small straight probe 407-1 and mounting ring PH 07-4; PeriMed) was used to measure blood flow through the pedicle in all groups. The Periflux 5010 Laser Doppler Perfusion Monitor unit was attached to the probe just before the start of the measurement through a simple holding frame to prevent signal errors. A laptop personal computer with PeriSoft for Windows software was used as a signal recorder. All of the values from the laser Doppler flowmeter were exported from the PeriSoft software into an ASCII text formatted file for each measurement. The sampling period was set up to $\tau = 0.03$ second.

Each measurement resulted in a blood perfusion signal, which showed flap perfusion dynamics for the typical shape of the signal (Fig. 3). Blood perfusion signals were described by two time intervals, which were extracted with the use of an automated signal delineation method. The first and the most clinically important parameter was vasospasm duration, the time interval during which the flap was not perfused because of persistent vasospasm. The second, rather auxiliary parameter was time to hyperperfusion, the time interval between the termination of stimulus and the time point when the highest hyperperfusion level was reached. Both parameters, vasospasm duration and time to hyperperfusion, were statistically compared between particular groups.

Signal Processing

The Savitzky-Golay polynomial filter was used to smooth the raw measured signals that were

Table 2. Timing of the Measurements

Time	Step of the Experiment
−45 min	Attachment of the probe fixation ring to the flap, beginning of dissection
−40 min	Flap left resting for next 25 minutes
−15 min	Attachment of the probe to the fixation ring and beginning of measurement of flap perfusion
−10 min	Beginning of script, measurement of basal level of flap perfusion
−5 min	Beginning of stimulation, hanging of 15-g weight, beginning of local application of drug by dropping or bolus intraperitoneal injection
0 min	Termination of the stimulation, continuous dropping, continuous measurement of perfusion
2 min	Termination of the dropping, continuous measurement of perfusion
30 min	Termination of the measurement, disconnection of the probe from the flap, and termination of the experiment

corrupted by impulse noise. This preprocessing step resulted in enhanced signals on which our algorithm for automated delineation of the signals was applied, to extract parameters relevant to the focus of our study. The delineation algorithm was designed and implemented in a form of a set of functions and scripts in Matlab (MathWorks, Inc., Natick, Mass.), so that it simulated analytical thinking of an expert providing manual delineation. Because of the remarkable high shape variability in the signals—mainly during the vasospasm and reperfusion phases (Fig. 4)—we were describing each signal by two time intervals as mentioned above. Whereas the time interval vasospasm duration represented duration of the vasospasm, the time interval time to hyperperfusion represented how rapid or slow flap reperfusion was. The other parameters described in Figures 3 and 4 represent various blood perfusion levels during each measurement. The most important one was the threshold blood perfusion level L_t, as it served for extracting the time interval vasospasm duration. The threshold L_t was determined as the sum of the blood perfusion level after stimulus termination (L_0) and the tenth of the reperfusion wave amplitude given by the difference between levels L_{hp} and L_s:

$$L_t = L_0 + \frac{L_{hp} - L_s}{10}, \qquad (1)$$

where L_s was determined as the tenth percentile of signal values during the stimulation of vasospasm, L_0 was determined as the tenth percentile of signal values after the end of stimulation and before the reperfusion wave reached half of its amplitude, and L_{hp} was determined as the median of signal values during 3 seconds around the time point in which the maximum blood hyperperfusion value was found. The median filtration was preferred before simple averaging, as the blood perfusion signal values were not normally distributed.

RESULTS

The vasodilatory effects of the drugs were evaluated in 14 groups and compared with the control group. Some of the 280 measurements had to be removed from further statistical processing: six measurements because of an excessive number of artifacts in the signals; three measurements because of errors in the stimulus application (operating personnel mistake); and three measurements because of partial absence of data (spontaneous shutdown of the recorder or the computer). No reperfusion was observed in the interval of 30 minutes after releasing the weight in 13 measurements, and the signals had atypical shapes as well. In such cases, time intervals were determined to be as follows for subsequent data processing: vasospasm duration, 30 minutes; and time to hyperperfusion, 60 minutes.

The existence of differences between the groups was tested by nonparametric analysis of variance (Kruskal-Wallis) tests. Significant differences in the time intervals were detected ($p = 1.034 \times 10^{-10}$ for vasospasm duration and $p = 1.772 \times 10^{-7}$ for time to hyperperfusion). It means that at least two of the group medians of the time intervals vasospasm duration and time to hyperperfusion differed significantly. Distributions of vasospasm duration and time to hyperperfusion values across the groups are shown in the box and whisker plots (Figs. 5 and 6).

Additional exploration of the differences between groups was needed to provide information, whether the medians were significantly different from each other. Post hoc Wilcoxon rank sum tests were used together with the Bonferroni method of correction for multiple comparisons. The results of the post hoc analysis are shown in Tables 3 and 4. The reported p values were determined according to the Bonferroni correction method multiplied by the total number of tests performed ($n = 105$), to prevent false-positive results.

Evaluation of Vasospasm Duration (Bonferroni Correction, $n = 105$)

Vasospasm duration was significantly shorter compared with the control group in groups 1

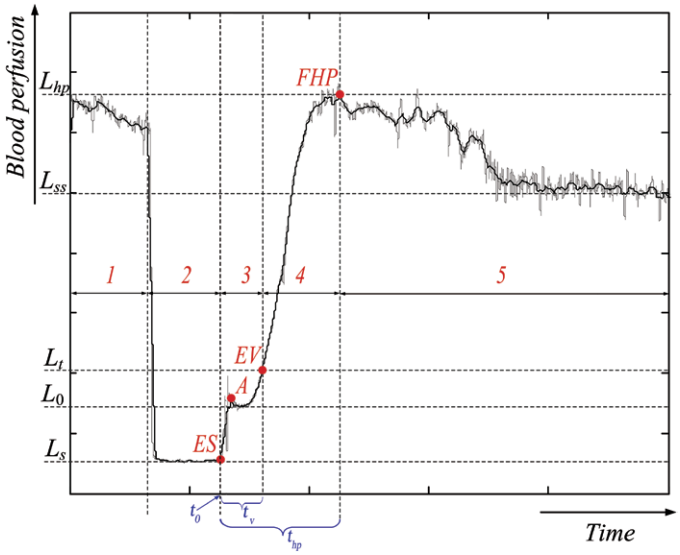

Fig. 3. Typical shape of the perfusion curve and extraction of the time intervals vasospasm duration and time to hyperperfusion. The following time intervals could be differentiated on the curve: *1*, resting perfusion in the flap after its dissection; *2*, segment of significantly reduced levels up to an arrest of perfusion of the flap was defined from the application of the stimulus to the vasospasm, applying the weight until it was released at the end of stimulus (point *ES*); *3*, the segment of significantly reduced perfusion, which represents persisting vasospasm of the vascular pedicle. At the beginning of this segment was regularly observed peak artifact (*A*) that developed by the movement of the probe until disconnection of the weight. At the end of this segment occurs restoration of flap perfusion and the curve changes at the end of vasospasm (point *EV*) into (*4*) a segment with a further increase of flap perfusion, which continues to maximal perfusion values at the point of flap hyperperfusion (*FHP*). The flap turned pink already at the lower third of the increasing part of the curve, whereas in the area of maximal values there was already compensatory hyperemia of the flap that manifested with redness (point *FHP*). *5*, Subsequently, slower stabilization of flap perfusion to the level of normal perfusion and pink color of the flap occurred. *Gray solid lines*, raw measured signals; *black solid lines*, signals after preprocessing; *gray dashed lines*, delineated signal levels (*horizontal*) and time intervals (*vertical*). A signal delineation algorithm was used to extract automatically the following parameters relevant to the study: L_s, blood perfusion level during vasospasm stimulation; L_0, blood perfusion level after stimulus termination; L_{hp}, the highest blood hyperperfusion level; L_{ss}, steady-state blood reperfusion level; t_0, termination of the vasospasm stimulus (recorded manually); t_v, time interval between stimulus termination and reperfusion wave onset, defined as point *ES* to point *EV*; t_{hp}, time interval between stimulus termination and the time point when the highest hyperperfusion level was reached, defined as point *ES* to point *FHP*.

(pentoxifylline administered parenterally), 7 (10% magnesium sulfate applied locally), and 13 (verapamil applied locally). Vasospasm was significantly longer in group 5 (2% lidocaine applied locally).

Evaluation of Time to Hyperperfusion (Bonferroni Correction, $n = 105$)

Time to hyperperfusion was significantly shorter only in group 7 (10% magnesium sulfate applied locally). The results mentioned

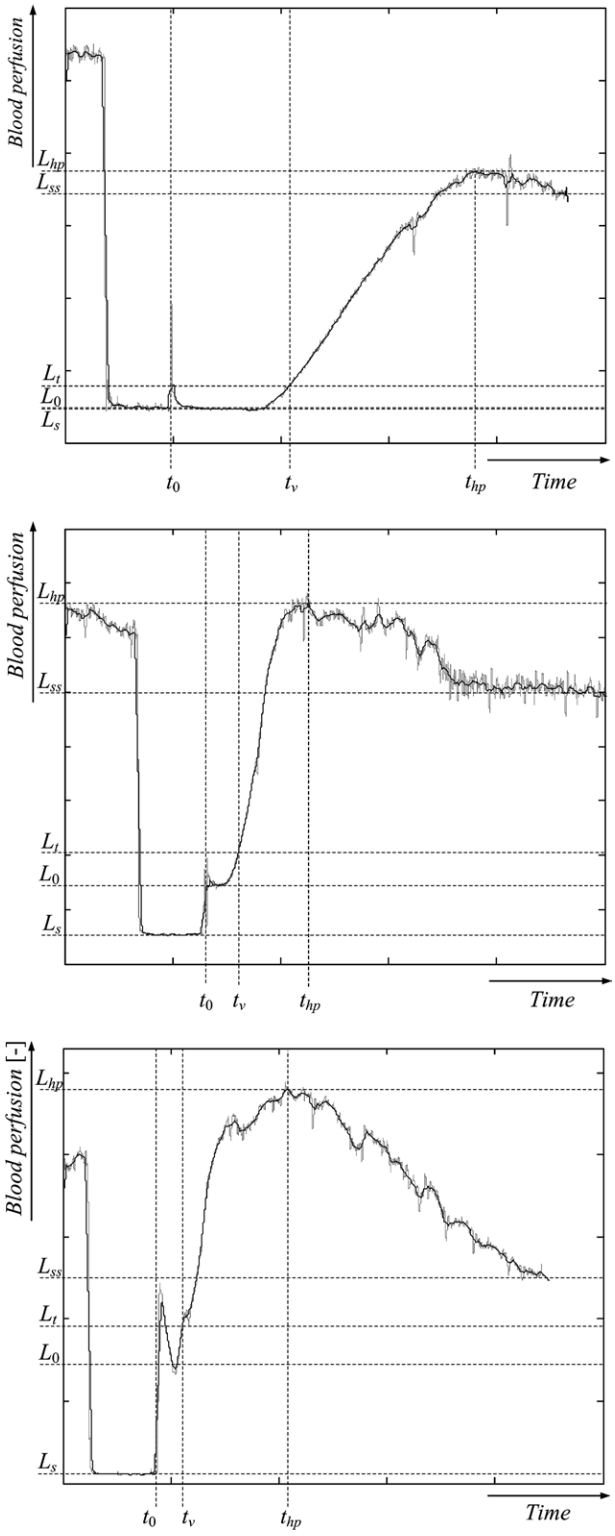

Fig. 4. Blood perfusion signal examples demonstrating the variability of perfusion parameters values (L_s, L_0, L_{hp}, L_{ss}, and L_t) in different subjects. It is also obvious that very similar duration of vasospasm time could be associated with very different times to hyperperfusion (*center* and *below*).

above were calculated using Bonferroni correction for all post hoc tests (n = 105) performed after nonparametric analysis of variance. If the groups with drug were compared only with the control group using the post hoc analysis performed with multiple Wilcoxon tests, more positive results were obtained, because Bonferroni correction was calculated for a lower number of tests performed (n = 14). The results of post hoc analysis, in which all drug groups are compared with one control group only, are reported in Table 5.

Evaluation of Vasospasm Duration (Bonferroni Correction, n = 14)

Vasospasm duration differed significantly from the control group in groups 1, 2, 5, 6, 7, 10, and 13 at the 5 percent significance level 5 and in groups 1, 5, 7, and 13 at the 1 percent significance level. Vasospasm duration was shortened in groups 1 and 2 (pentoxifylline applied parenterally and locally), 6 and 7 (10% magnesium sulfate applied parenterally and locally), 10 (1% trimecaine applied locally), and 13 (verapamil applied locally), and prolonged in group 5 (2% lidocaine applied locally).

Evaluation of Time to Hyperperfusion (Bonferroni Correction, n = 14)

The time to hyperperfusion in groups 5 and 7 differed significantly from the control group at the 5 percent significance level. Time to hyperperfusion was longer in group 5 and shorter in group 7.

DISCUSSION

The pathogenesis of vascular complications in microsurgery is often a complex process in which three basic pathologic entities may play different roles: thrombosis, ischemia reperfusion injury or the no-reflow phenomenon, and vasospasm. One pathologic entity is frequently manifested more than the other. The personal experience of the microsurgeon seems to be the most important factor in management of the vascular complication and in specific therapy selection. The most often used drugs in the prevention and treatment of vascular complications include antiaggregants and anticoagulants. Others are used less frequently. In certain cases, the selection of a proper pharmacologic management that is specifically focused on vasospasm may save flap vitality.

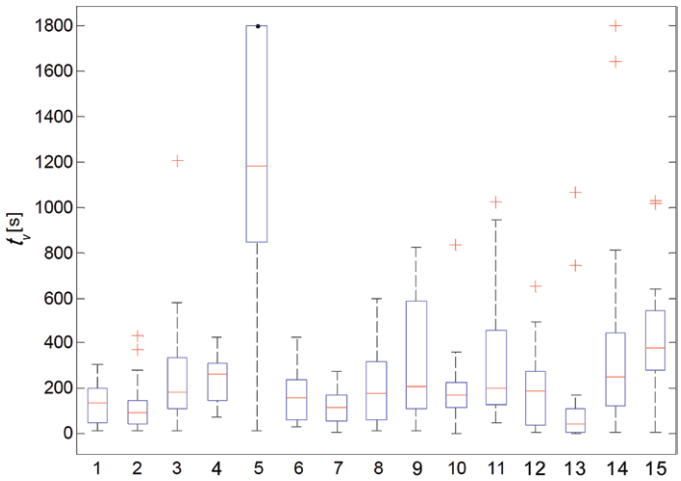

Fig. 5. Distributions of the time interval vasospasm duration (t_v) values across the groups. On each box, the *central mark* is the median, the *edges of the box* are the 25th and 75th percentiles, the *whiskers* extend to the most extreme data points not considered outliers, and outliers are plotted individually.

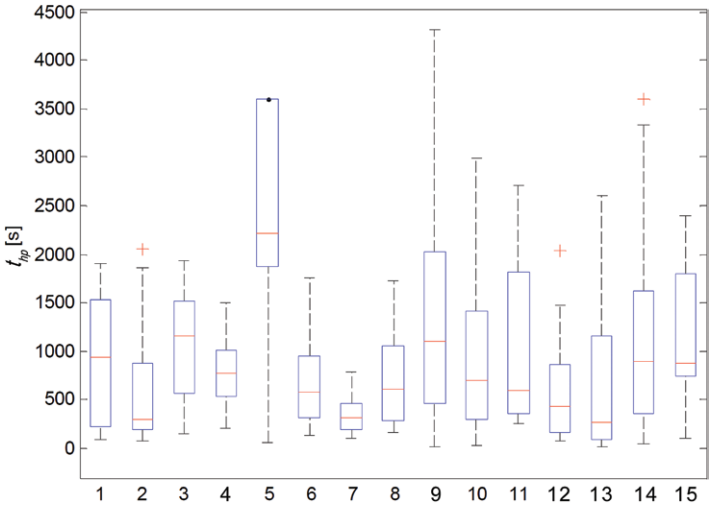

Fig. 6. Distributions of the time interval time to hyperperfusion (t_{hp}) values across the groups. On each box, the *central mark* is the median, the *edges of the box* are the 25th and 75th percentiles, the *whiskers* extend to the most extreme data points not considered outliers, and outliers are plotted individually.

An ideal pharmacologic agent should act in the pedicle and in the microcirculation of a flap, even after topical application.[14] A considerable number of medicaments are routinely used in clinical practise. Their efficacy on surgically induced vasospasm has been disputable in all of the cases. Differentiation of vasospasm that subsides spontaneously from that resulting from a specific therapy seems to be difficult in clinical practice. This was the main reason for creating this study, with a primary aim of comparing the effect of different commonly available vasodilating drugs on surgically induced vasospasm. The goal of subsequent analysis was to select those that are effective and also to choose the most effective one. To achieve this, we compared the distributions of vasospasm duration and time to hyperperfusion between all groups and to the distributions of the time parameters in the control group.

Pentoxifylline applied parenterally and 10% magnesium sulfate and verapamil applied locally were evaluated as the most potent vasodilators.

Table 3. Results of Post Hoc Wilcoxon Tests for Vasospasm Duration Showing Statistically Significant Differences between Specific Groups*

	Group													
Group	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
1	1	1	0.382	0.005†	1	1	1	1	1	1	1	1	1	0.037†
2		1	0.194	0.003†	1	1	1	1	1	0.260	1	1	1	0.163
3			1	0.020†	1	1	1	1	1	1	1	0.116	1	1
4				0.016†	1	0.032†	1	1	1	1	1	0.006†	1	0.785
5					0.006†	0.003†	0.005†	0.018†	0.008†	0.047†	0.004†	0.001†	0.091	0.045†
6						1	1	1	1	1	1	0.914	1	0.360
7							1	0.804	1	0.142	1	1	0.950	0.023†
8								1	1	1	1	0.566	1	1
9									1	1	1	0.184	1	1
10										1	1	0.836	1	0.237
11											1	0.009†	1	1
12												1	1	0.381
13													0.107	0.041†
14														1

*The reported *p* values were corrected with the Bonferroni method (i.e., multiplied by the total number of tests performed; $n = 105$).
†Significant differences.

Table 4. Results of Post Hoc Wilcoxon Tests for the Time to Hyperperfusion Showing Statistically Significant Differences between Specific Groups*

	Group													
Group	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
1	1	1	1	0.017†	1	1	1	1	1	1	1	1	1	1
2		1	1	0.01†	1	1	1	1	1	1	1	1	1	1
3			1	0.02†	1	0.026†	1	1	1	1	1	0.960	1	1
4				0.01†	1	0.008†	1	1	1	1	1	1	1	1
5					0.01†	0.002†	0.009†	1	0.030†	0.080	0.008†	0.002†	0.182	0.207
6						0.785	1	1	1	1	1	1.0	1	1
7							1	0.111	1	0.1172	1	1	0.382	0.026†
8								1	1	1	1	1	1	1
9									1	1	1	1	1	1
10										1	1	1	1	1
11											1	1	1	1
12												1	1	1
13													1	1
14														1

*The reported *p* values were corrected with the Bonferroni method (i.e., multiplied by the total number of tests performed; $n = 105$).
†Significant differences.

Although medians for vasospasm duration and time to hyperperfusion for verapamil and pentoxifylline were shorter than medians for 10% magnesium sulfate, differences expressed in *p* values were more significant for 10% magnesium sulfate than for verapamil and pentoxifylline and were also the most significant of all. This is true for both parameters (vasospasm duration and time to hyperperfusion) and for both Bonferroni corrections. Therefore, the efficiency of 10% magnesium sulfate applied locally can be considered as the most reliable.

Magnesium sulfate is used especially by neurologists and neurosurgeons in the treatment of cerebral vasospasm and other diseases.[15–18] However, the positive effect of magnesium sulfate has not yet been reliably demonstrated in microsurgery. The mechanism of action of magnesium sulfate has not been clarified, although its vasodilating features have been well described in vitro[19–22] and in vivo.[23–26]

Pentoxifylline is a xanthine derivative that activates smooth muscle relaxation directly or by inhibition of phosphodiesterase. Improvement of skin-flap survival was observed after using pentoxifylline in rats.[27,28] We used pentoxifylline empirically several times parenterally after free flap transfer, with a promising effect on relieving vasospasm; this treatment was well tolerated by the patients.

Nimodipine (L-type calcium channels) improves flap survival in randomized experimental

study in rats.[29] Weinzweig et al. compared the effect of verapamil and nifedipine on vasospasm induced by cold. Verapamil was evaluated as more effective.[30] Verapamil seems to be less suitable for wider clinical use because of its cardiac side effects.

Lidocaine and other local anaesthetics have often been used as vasospasm-relieving therapy. Several studies confirmed local and dose-dependent vasodilating effect of lidocaine.[31–34] Beekman et al. examined the effect of lidocaine in different concentrations on the vasospasm of rat-tail artery induced by local administration of ergotamine. The efficacy of lidocaine increased proportionally up to the concentration of 12%. Clinically most often used 2% lidocaine had just a slight vasodilating effect, and tissue toxicity was observed after the use of 20% lidocaine.[33] Ohta et al. compared the vasodilating effect of lidocaine in concentrations of 2%, 4%, 10%, 20%, and 40%. Vasospasm of the rat femoral artery was produced by administration of fresh blood from another rat. They did not find any effect of 2% lidocaine; its efficiency gradually increased up to the concentration of 20%.[34] Kim et al. demonstrated the vasodilating potential of 2% lidocaine, which is a concentration used clinically, in the porcine gastroepiploic artery.[35] In contrast, the article by Evans et al.[14] confirmed that 2% lidocaine acts as a spasmolytic agent in a rabbit carotid model. The safety-related dose of lidocaine is disputable, although Johnstone et al. demonstrated the safety of topical use of 4% lidocaine in microsurgical procedures.[36] The local anaesthetics tested in our study, except for trimecaine, did not cause significant shortening of vasospasm duration or time to hyperperfusion. In our study, 2% lidocaine even significantly prolonged vasospasm duration. We can conclude that local anesthetics with the exception of trimecaine have only a minor vasodilating effect on surgically induced vasospasm. We assume that the use of 2% lidocaine as a spasmolytic agent should be reevaluated in microsurgery.

Wang et al. studied the action of sodium nitroprusside on vasospasm induced by ischemia and reperfusion within the circulation of the cremaster muscle in a rat. Sodium nitroprusside was evaluated as a potent spasmolytic agent.[37,38] Price and Pearl studied the effect of locally applied nitroglycerin cream and intravenous allopurinol on an excessively long skin flap in a rat. Both medicaments enhanced flap survival separately, but their combination did not lead to higher parameters of flap survival.[39] The effect of local application of nitroglycerin had been disputable in other experimental studies.[40,41] The effectiveness of papaverine was examined and confirmed in several comparative experimental studies.[14,32,42]

Alprostadil (prostaglandin E_1) is a potent vasodilator and antiaggregant. Chen et al. confirmed its ability to relieve vasospasm and compared it with 1% lidocaine in the rabbit.[43]

The use of the automated delineation algorithm prevented us from another source of measurement uncertainty and thus ensured maximum objectivity and accuracy in obtaining the values of the two parameters vasospasm duration and time to hyperperfusion selected to describe the signals. An alternative use of only one time interval to extract the useful information from the signals would result in the inability to distinguish between the duration of vasospasm and the flap reperfusion speed. The nonredundancy of our signal description is also demonstrated in the example signals (Fig. 4). Nearly the same short duration of vasospasm in the examples shown in Figure 4, *center* and *below* do not necessarily imply the same reperfusion speed (time to hyperperfusion) of the flaps. However, the time interval vasospasm duration was considered in our study to have a higher importance in comparison of lengths of vasospasm.

Perfusion of the flap near level L_t on the perfusion curve could be considered sufficient for survival of the flap with regard to the clinical correlation with the color of the flap (the

Table 5. Results of Post Hoc Wilcoxon Tests for Vasospasm Duration and Time to Hyperperfusion Showing Statistically Significant Differences between Control Group and Particular Drug Groups*

	p	
Group	t_v	t_{hp}
1	0.0050†	1
2	0.0218†	0.2579
3	0.5501	1
4	0.1046	3.1504
5	0.0060†	0.0276†
6	0.0480†	0.8987
7	0.0030†	0.0034†
8	0.1474	0.8875
9	1	1
10	0.0316†	1
11	2.1870	1
12	0.0508	0.2222
13	0.0054†	0.3487
14	4.0031	1

t_v, vasospasm duration; t_{hp}, time to hyperperfusion.
*The reported *p* values were corrected with the Bonferroni method (i.e., multiplied by the total number of tests performed; $n = 14$).
†Significant differences.

flap was turning pink). At level L_{hp}, the flap was red and compensatory hyperemia was observed. At level L_{ss}, perfusion of the flap was already optimal. The time when the flap achieves this hyperperfusion (time to hyperperfusion) is influenced not only by the duration of vasospasm but also by metabolic and other factors. Therefore, two different flaps with the same duration of vasospasm could have different values of time to hyperperfusion (Fig. 4). This corresponds also to a higher variability of the parameter time to hyperperfusion compared with vasospasm duration (Figs. 5 and 6). The time interval vasospasm duration therefore corresponds to the duration of vasospasm, whereas the parameter time to hyperperfusion shows the time required to achieve the peak of compensatory mechanisms.

CONCLUSIONS

Drugs that reduce the duration of vasospasm in experimental model conditions after its induction by axial tension most effectively ($p < 0.05$) include the following (Table 5): 10% magnesium sulfate applied locally, pentoxifylline applied parenterally, and verapamil applied locally. The following drugs are also effective: pentoxifylline applied locally, 10% magnesium sulfate applied parenterally, and 1% trimecaine applied locally. Significant prolongation of vasospasm was observed after administration of 2% lidocaine.

The most effective drug was 10% magnesium sulfate applied locally, which shortened the vasospasm duration most significantly ($p = 0.0030$) and the time to hyperperfusion ($p = 0.0034$) (Table 5). Therefore, we used 10% magnesium sulfate for subsequent experiments in an analogic porcine model to verify its effectiveness.

Although we cannot draw any general conclusions for human medicine, this study may help microsurgeons to review their opinion regarding pharmacologic treatment of vasospasm and perhaps incorporate magnesium sulfate into the protocols for therapy of vasospasm in the future. In contrast, we assume that the use of 2% lidocaine as a spasmolytic agent should be reevaluated in microsurgery.

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