

Comparative study of vasodilatation after intra-arterial nicardipine or dantrolene infusion in animal model of cerebral vasospasm

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Abstract

Intra-arterial (IA) infusions of calcium channel blockers (CCBs) have been widely applied in treating medically refractory vasospasm. However, surprisingly little is known regarding their vasodilatory duration. This study was undertaken to compare attributes of nicardipine and dantrolene, focusing on efficacy and capacity for sustained vasodilation. In New Zealand white rabbits (N=22), vasospasm was individually provoked through experimentally induced subarachnoid hemorrhage and confirmed via conventional angiography, grouping animals by IA-infused drug (nicardipine vs dantrolene). Controls received normal saline. After chemoangioplasty, follow-up angiography was performed at intervals of 1-3 hours for 6 hours to compare vasospastic and dilated (ie, treated) arterial diameters. Drug efficacy, duration of action, and changes in mean arterial pressure (relative to baseline) were analyzed by group. Compared with controls, effective vasodilation was evident in both nicardipine and dantrolene test groups after IA infusion. Vasodilatory effects of nicardipine peaked at 1 hour, returning to former vasospastic states at 3 hours. In dantrolene recipients, vasodilation endured longer, lasting >6 hours. This outcome suggests that IA dantrolene infused alone or together with a conventional CCB infusion may be a new means of prolonging vasodilatory effect. Further research is needed to assess durations of IA-infused vasodilatory drug based on perfusion status.

Introduction

Although surgical and endovascular treatments of cerebral aneurysms have rapidly advanced, morbidity and mortality currently remain unchanged due to vasospasm. The etiology of vasospasm is not entirely clear, and there are no definitive therapies as yet to resolve severe symptomatic states, preventing delayed cerebral ischemia. A conservative remedy for vasospasm is thus a high priority.

Oral nimodipine is the only medical intervention to date with proven efficacy for vasospasm.¹⁻³ In practice, however, various alternatives for vasodilation (eg, chemical angioplasty by intra-arterial [IA] or intrathecal drug infusion and mechanical angioplasty via balloon or retrievable stent) have been implemented for severe symptomatic vasospasm refractory to medical treatment.²⁻⁴ Calcium channel blockers (CCBs) are the preferred IA agents at present for chemical angioplasties, as many reports on safety and efficacy will attest.^{2,3,5-14} Nevertheless, the limitations of IA-infused CCBs, particularly their duration of action, have raised concerns. Some patients with severe vasospasm seem to experience neurologic deterioration within hours after IA drug-infused recovery, necessitating two or three daily treatments. The short-lived vasodilation that IA-infused CCBs afford may be responsible. Lim et al.¹⁵ have reported that in an animal model of vasospasm, such effects were not sustained more than 2 hours after IA infusion.

Dantrolene is a known ryanodine receptor (RyR) inhibitor, already FDA approved for treating malignant hyperthermia and muscle spastic disorder. Its mechanism of action on smooth muscle cells differs from that of CCBs. Ortiz Torres et al.¹⁶ have suggested that IA-infused dantrolene is a safe and effective novel treatment option for vasospasm, reporting its use in two patients. The present investigation was

launched to examine characteristics of nicardipine (a CCB popular in IA chemoangioplasty) and dantrolene. A rabbit animal model enabled side-by-side comparisons of these agents, based on angiographic assessments of vasodilatory efficacy and duration.

Materials And Methods

Animal selection and preparation

The study protocol complied with provisions of our institutional committee for ethical animal experimentation and was granted approval. We selected 35 commercially available New Zealand white rabbits (weights, 2.5-3.0 kg) for testing. In a fasted state (6 hours prior), each animal received a dual-agent (ketamine, 35 mg/kg; xylazine, 5 mg/kg) anesthetic intramuscular (IM) injection of the thigh, supplemented at 20-min intervals during procedures as needed. Depilatory cream removed inguinal and occipital hair under anesthesia. Each rabbit was then secured supine to the examination table. All were subjected to skin testing and given IM injections of a first-generation cephalosporin (50 mg/day) for 3 days after experiment completion.

Puncture of femoral artery and introducer insertion

We sterilized (75% alcohol) inguinal regions of anesthetized animals, each positioned as above. Femoral artery was palpated and exposed within its neurovascular bundle, making an inguinal incision (~20 mm) under local anesthesia (1% lidocaine). Next, a 4-Fr introducer was installed (Seldinger technique) via femoral artery puncture and secured to femoral artery, filling it with heparin/normal saline solution for subsequent transducer passage. Blood pressure (BP) readings were thereby obtained. At completion of cerebral angiography, introducers were secured within subcutis (5-0 nylon skin suture) to facilitate follow-up angiography 3 days after inducing SAH.

SAH induction in animal model

Occipital regions of anesthetized animals (positioned supine, 90° left-rotated heads) were sterilized (75% alcohol). Contiguous occipital-cervical areas were epilated and heads bent for puncture of dura mater under local anesthesia (1% lidocaine) and with fluoroscopic guidance, using a 23-G spinal needle to pierce atlanto-occipital membranes. To identify subarachnoid space, cisternal delivery of mixed contrast medium and normal saline (1:1 ratio) commenced at first sign of cerebrospinal fluid (CSF). A modicum (~2 cc) of CSF was then withdrawn, instilling a 2-cc sampling of femoral arterial blood as replacement via spinal needle. Thereafter, animal heads were lowered (~30°) and allowed 20 min of stabilization.^{12,14} Angiography equipment (Allura Xper FD20/10; Philips Healthcare, Amsterdam, Netherlands) used for Xper computed tomography (CT) enabled verification of SAH.

Cerebral angiography and IA drug infusion

Cerebral angiography (Allura Xper FD20/10; Philips Healthcare) entailed iso-osmolar contrast delivery. For IA drug infusion, microcatheters (Excelsior SL-10; Stryker Neurovascular, Fremont, CA, USA) and microguidewires (Synchro14; Stryker Neurovascular) were engaged. Routine angiographic assessments of vertebral and basilar arterial diameters at baseline (ie, before SAH induction) provided reference points for later comparisons. Angiography was repeated on Day 3 of the SAH model to confirm basilar arterial vasospasm, defined as >30% luminal compromise relative to baseline level. Luminal constriction <30% was disqualifying, eliminating animals from further involvement. Rabbits demonstrating vasospasm of acceptable level were then randomly assigned to IA therapeutics as follows: group N, nicardipine (0.06 mg/kg); group D, dantrolene (1 or 2 mg/kg); or group C, normal saline controls.

Established dosing of nicardipine, known to exert maximum physiologic effects in terms of arterial vasodilation, was applied herein.^{17,18} Loading/maintenance dosing of dantrolene seemed to be in the range of 1 or 2 mg/kg. Each IA agent was separately admixed with normal saline for microcatheter infusion in a period of 10 min. A 20% drop in BP (relative to baseline) warranted 50% dose reduction, any further decline calling for cessation. Once administered, immediate therapeutic effects were determined by extent of vasospastic easing at points of maximal luminal compromise. Follow-up angiography was pursued at intervals of 1-3 hours for a total of 6 hours, tracking luminal magnitudes (**Figure 1**) to monitor potential vasospastic reversions.

Angiographic gauging of arterial diameters

Arterial diameters (of basilar artery primarily) were assessed using a proprietary double-blind computer application (Vascular Quantification Software; Philips Healthcare) designed for cerebral angiography. Images selected were in arterial phase, least prone to motion artifact, measuring magnitudes in transverse plane. Two investigators, blinded to any pertinent input, measured diameters of normal and most severely vasospastic arteries, recording the average of two measurements taken at respective time intervals. Grading of luminal spasm reflected percent compromise in arterial diameter (relative to baseline), vasospastic reversal percentage corresponding with vasodilatory effect after IA infusion.

Diameter of artery at specific time point after vasospasm

Diameter (%) = _____

Baseline diameter of artery (before vasospasm)

Statistical analysis

Continuous variables were expressed as median and range values. The Wilcoxon signed-rank test was used accordingly for pairwise analysis of vasodilatory effects and change in BP change after IA infusion. To compare group vasodilatory effects, durations of action, and BP changes after IA infusion, the Kruskal-Wallis test was applied, invoking the Bonferroni correction for multiple comparisons of statistically significant outcomes. A linear mixed model (LMM) served to identify associations of time effect, group effect, and interaction between the two. Group pairwise comparisons were conducted through LMM. Above analytics were powered by standard software (SAS v9.4; SAS Institute, Cary, NC, USA). All tests were 2-sided, with .05 denoting statistical significance.

Result

Data summary

The 35 rabbits initially selected suffered nine deaths and eight induction failures (insufficient vasospasm), leaving 18 animals for our three experimental groups (each n=6). There were no instances in which BP declines forced interruption of drug infusion. Compared with baseline status (prior to SAH), the overall median for vasoconstriction of basilar artery was 54.7% (range, 36.6-62.5%) in this animal model of vasospasm. Groupwise medians were as follows: nicardipine, 55.3% (range, 36.6-60.6%); dantrolene, 49.0% (range, 36.9-61.2%); and controls, 61.7% (range, 47.2-62.5%). See **Table 1** for summary of data.

Efficacy of IA CCB infusion

Upon induction of vasospasm, changes in diameters of basilar arteries (relative to baseline levels) were measured immediately and at 1-3 hour intervals after IA infusion (**Table 1**). Immediate vasodilatory effects were regularly noted (group N, 35.1%; group D, 49.4%), showing statistical significance ($p=0.031$ and $p=0.031$, respectively) in both test groups, compared with controls (no vasodilation). Repeat angiograms at 1 hour indicated peak vasodilation in group N (51.5%; $p=0.031$) and sustained vasodilation in group D (40.8%; $p=0.031$). At 3 hours, significant vasodilation remained in group D (57.3%; $p=0.031$), having dissipated in group N and returned to former vasospastic states. At 6 hours, vasodilatory effect persisted in group D only (**Figure 2**). **Supplementary Table 1** shows differing pairwise time frames for each group in the LMM. Estimates of least square means and p -values are shown, adjusted using Bonferroni correction.

In groupwise comparisons of maximum vasodilatory efficacy, both agents achieved similar effects immediately and at 1 hour after IA infusion. Subgroup analysis of group D revealed that dantrolene at higher dose (2 mg/kg) outperformed the lower dose (1 mg/kg) in terms of potency (**Figure 3**). However,

statistical significance was not reached, given so few animals (**Supplementary Table 2**). Vasodilation in group D (either dose) lasted >6 hours, enduring for <3 hours in group N.

Mean arterial pressure flux during and after IA drug infusion

BP decline was observed during and after IA infusion of nicardipine (group N), an average loss of 10 mmHg recorded within 1 hour after administration. There was gradual recovery after 2 hours, with normalization after 3 hours. Almost no change in BP was evident after IA infusion of dantrolene (groups D) or in saline-infused controls (group C).

Discussion

Cerebral vasospasm in conjunction with subarachnoid hemorrhage (SAH) of ruptured aneurysms has been associated with delayed cerebral ischemia and currently is deemed the largest contributor to morbidity and mortality in this setting. The therapeutic imperative for treating vasospasm after SAH is preservation of cerebral blood flow, ostensibly through acceptably sustained central perfusion pressures. Although the mechanisms responsible for delayed cerebral ischemia are not fully understood, a critical issue reportedly is cellular influx of calcium.^{7,19} CCBs serve to suppress this influx, which is key in preventing and treating vasospasm and explains why oral intake of nimodipine is strongly advised.² As IA-infused agents of chemoangioplasty, they have been used for some time to treat severely symptomatic patients refractory to medical remedies, amassing an abundance of evidentiary support during the past three decades.

In practice, we have often observed that many patients improve clinically and angiographically after IA CCB infusion. However, the chief limitation of such intervention is durability of vasodilatory effect. Specifically, there is no consensus on how long the vasodilation of IA chemoangioplasty is sustained or how frequently chemoangioplasty must be performed to avoid cerebral ischemia. Lim et al.¹⁵ have already determined that more than 2 hours after IA infusion, CCB vasodilatory effects are lacking in an animal model of vasospasm.

Dantrolene is a RyR blocker approved for treatment of malignant hyperthermia, chronic spasticity, and neuroleptic malignant syndrome.^{20,21} Its mechanism of action differs from that of CCBs. Vasospasm is related to vascular tone, based on persistent elevation of intracellular Ca⁺⁺ in vascular smooth muscle.²² This rise in intracellular Ca⁺⁺ may be secondary to increased entry of extracellular Ca⁺⁺ upon activation of L-type voltage-dependent Ca⁺⁺ channels²³ or to heightened RyR release of Ca⁺⁺ from sarcoplasmic reticulum. CCBs are L-type channel blockers, whereas dantrolene imposes RyR blockade. Salomone et al.²⁴ have therefore suggested that combined use of these drugs may reduce both incidence and severity of vasospasm, achieved by dual activity. Moreover, both dantrolene and CCBs exert neuroprotective effects through increased antioxidant defense.²⁵

In rabbits with induced vasospasm, we have demonstrated that the vasodilatory effect of dantrolene (>6 hours) significantly outlasts that of IA-infused nicardipine (<3 hours) after IA infusion. According to Lim et al.,¹⁵ neither nicardipine nor nimodipine show sustained vasodilation more than 2 hours after IA infusion. Intravenous (IV) nicardipine has a rapid onset of action (major effects, 10-15 min; plasma elimination half-life, 40-60 min); but its plasma concentrations decline triexponentially once infusion is ceased, displaying rapid early distribution (α -half-life, 2.7 min), an intermediate phase (β -half-life, 44.8 min), and a slow terminal phase (γ -half-life, 14.4 hours) detectable only after long-term infusion. This means that its onset is quick, and its duration of action is relatively short. Dantrolene, on the other hand, has a comparatively longer half-life (~12 hours according to available data). In adults, cumulative IV dosing of 2.2-2.5 mg/kg produces steady plasma concentrations for >5 hours.²⁶ Majidi et al.²⁷ and Ortiz Torres et al.¹⁶ have claimed in separate case reports that IA dantrolene infusion appears safe and effective in treating refractory vasospasm, affirming that its vasodilatory effect may exceed 24 hours (based on 24- and 48-hour follow-up angiography). However, these publications involved just one or two patients and 1- or 2-day follow-up studies, failing to pinpoint vasodilatory limits with precision. To our knowledge, the present effort is the first to directly compare a CCB with dantrolene in terms of vasodilatory capacity and duration, using an animal model of cerebral vasospasm. Ultimately, we have demonstrated that the vasodilatory effect of dantrolene (>6 hours) endures significantly longer than that of nicardipine (<3 hours).

There are a few reports in which single-dose IV dantrolene (1.25 or 2.5 mg/kg) given to patients with cerebral vasospasm (after SAH) significantly reduced spasm and aided in patient recovery.^{28,29} Regarding the safety of dantrolene, Muehlschlegel et al.³⁰ have found IV dantrolene (1.25 mg/kg) treatment of vasospasm to be feasible, tolerable, and safe in a randomized, double-blind, and placebo-controlled trial. Investigations by Majidi et al.²⁷ and Ortiz Torres et al.¹⁶ also support the efficacy of IA dantrolene infusion for refractory vasospasm at dosages of 15-30 mg (<1 mg/kg) in adult patients. In our study, we administered dantrolene at 1 or 2 mg/kg, having no real dosing standards for IA infusion. Its vasodilatory effect seemed dose-dependent (greater potency at 2 vs 1 mg/kg), proving similar to nicardipine (at maximum-effect dosage) when administered at 2 mg/kg. However, duration of action was the same (>6 hours) for both dantrolene subsets. Roman et al.²² have likewise shown in a rat model that improved endothelial-dependent relaxation and reduced vascular contractility conferred by dantrolene are dose-dependent phenomena. Given our findings, we feel that dantrolene alone or added to a conventional CCB for IA infusion may offer a new means of prolonging vasodilatory relief in patients with cerebral vasospasm.

This study has some acknowledged limitations. We equated the presence of vasospasm, as well as its degree or later improvement, with the most severe points of arterial compromise. Because the vasodilatory effects of IA-infused drugs impact both large arteries and small arterioles, such measurements may not reflect actual perfusion states. We must also concede that the number of animals servicing this experiment was marginal for three-group comparison. In addition, there are no established dosing equivalencies for treating cerebral blood vessels with these medications, and studies

focused on drug potencies have generated conflicting results. Hence, the IA drug dosages used for comparison herein may not be equivalent. Finally, we magnified photoimages to determine basilar arterial diameters, making it difficult to distinguish boundaries of small vessels and perhaps introducing measurement errors. In aggregate, these drawbacks are considerable and should be appropriately resolved going forward.

Conclusion

In a rabbit model of cerebral vasospasm, both nicardipine and dantrolene achieved effective vasodilation after IA drug infusion. However, the vasodilatory action of IA-infused CCB proved significantly shorter in duration (<3 hours) than that of IA-infused dantrolene (>6 hours). Thus, dantrolene alone or combined with a conventional CCB for IA infusion may be a reasonable means of prolonging vasodilatory action. Further study is needed to determine duration of IA-infused vasodilatory drugs based on perfusion status.

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Declarations

Conflict of interest We declare that we have no conflict of interest.

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Data availability: Any additional information will be provided after an appropriate request.

Author contributions

Cho YD: Conception and Design; Lim JW and Byoun HS: Analysis and Interpretation; Lim JW and Byoun HS: Data Collection; Lim JW: Wrote the main manuscript; Cho YD: Critical Revision; Lim JW and Cho YD: Statistical Analysis; All authors reviewed the manuscript.

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Tables

Table 1. Comparison of basilar arterial diameters before and after intra-arterial drug infusion, shown by time frame and group

Time	Group						Comparison of the diameter between groups	
	C group (n=6)	p value [†]	N group (n=6)	p value [†]	D group (n=6)	p value [†]		
	Med(Min,Max)		Med(Min,Max)		Med(Min,Max)		p value ^{††}	adjusted p value ^{**}
Spasm	61.7(47.2,62.5)		55.3(36.6,60.6)		49.0(36.9,61.2)		0.109	-
IADI	57.2(48.6,63.2)	1.000	74.7(73.0,82.1)	0.031	73.2(65.6,75.0)	0.031	0.002	C vs N=0.015 , C vs D=0.015
1hr	56.6(45.8,60.8)	0.313	83.8(64.6,100.0)	0.031	68.9(61.9,79.2)	0.031	0.002	C vs N=0.015 , C vs D=0.015
3hr	51.7(45.8,60.3)	0.156	54.6(44.6,89.2)	0.625	77.1(61.9,85.9)	0.031	0.018	C vs D=0.015
6hr	55.2(44.4,64.7)	0.656	51.7(44.6,59.2)	1.000	73.2(61.9,87.5)	0.031	0.004	C vs D=0.024 , N vs D=0.015

C group: Normal saline group, N group: Nicardipine group, D group: Dantrolene group

* IADI immediately after intra-arterial drug infusion, Med Median value, Min minimal value, Max maximal value

† p value by Wilcoxon signed rank test

†† p value by Kruskal-Wallis test

** Level of significance was adjusted with Bonferroni correction for multiple comparisons (Wilcoxon rank sum test)

Figures

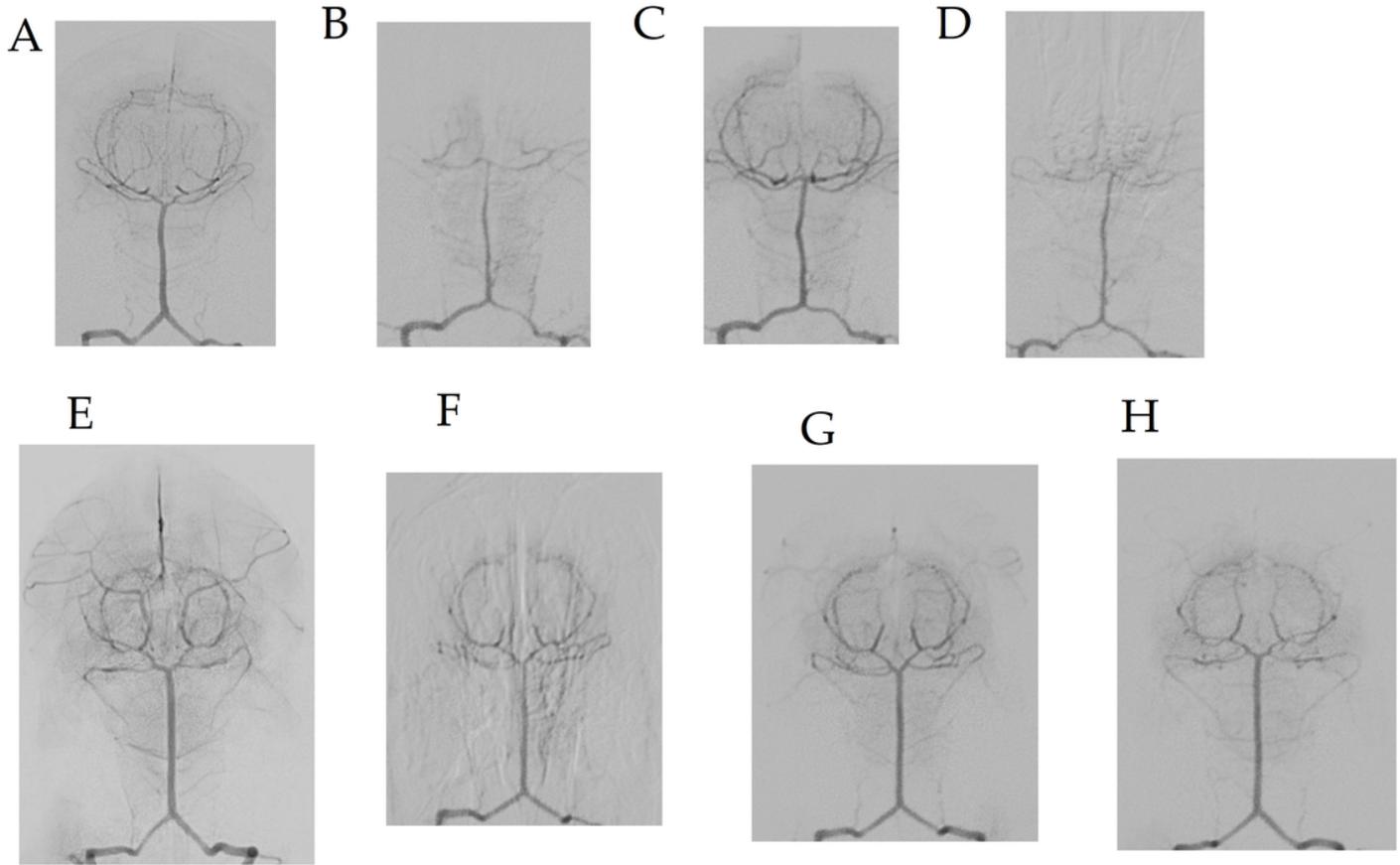


Figure 1

Digital subtraction angiograms of vertebrobasilar artery in rabbits over time (nicardipine group, A-D; dantrolene group, E-H): (A) Angiographic image prior to hemorrhage; (B) Follow-up angiographic image 3 days after subarachnoid hemorrhage (vasospasm); (C, D) Angiographic images 1 and 3 hours after intra-arterial (IA) drug infusion; (E) Angiographic image prior to hemorrhage; (F) Follow-up angiographic image 3 days after subarachnoid hemorrhage (vasospasm); and (G, H) Angiographic images 3 and 6 hours after IA drug infusion.

Luminal diameters of arteries after IA drug infusion

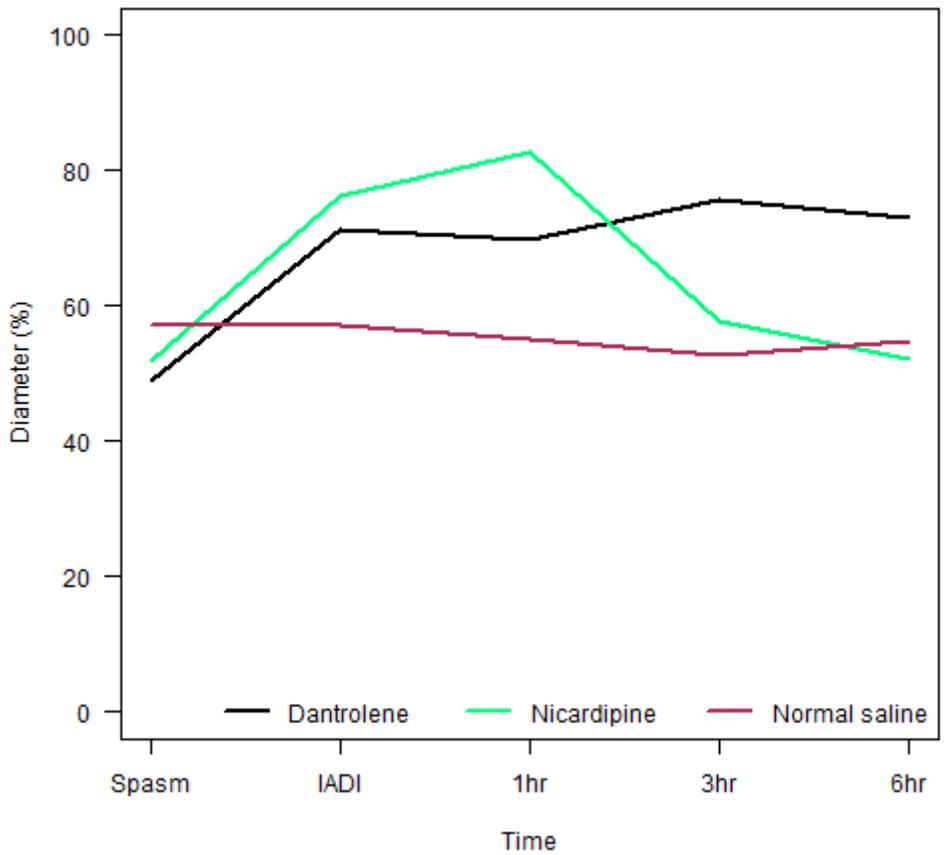


Figure 2

Groupwise comparison of basilar arterial diameters before and after intra-arterial drug infusion

Luminal diameters of arteries after IA drug infusion

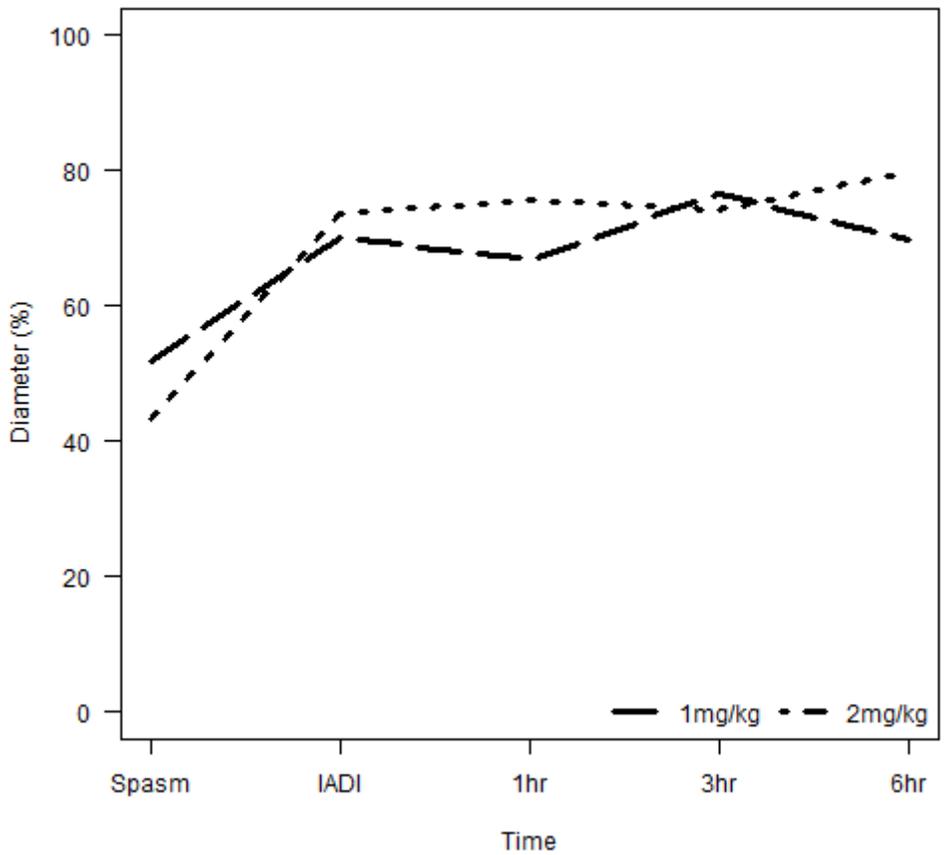


Figure 3

Subgroup comparison of basilar arterial diameters before and after intra-arterial infusion of dantrolene

Supplementary Files

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