Investigation of the role of infusate properties related to midline catheter failure in an ovine model

Marcia Ryder, PhD, MS, RN, Ryder Science Inc., Brentwood, TN

Robert A. Gunther, PhD, MA, University of California, Davis, Davis, CA

Reid A. Nishikawa, PharmD, BCNSP, FASPEN, FCSHP, Nutrishare, Inc., Elk Grove, CA

Marc Stranz, PharmD, StranzCrossley Inc, Weston, FL

Britt M. Meyer, RN, PhD, CRNI, NE-BC, VA-BC, Duke University Hospital, Durham, NC, and East Carolina University School of Nursing, Greenville, NC

Taylor A. Spangler, DVM, DACVP, VDx Veterinary Diagnostics and Preclinical Research Services, Davis, CA

Albert E. Parker, PhD, MS, Center for Biofilm Engineering, Department of Mathematical Sciences, Montana State University, Bozeman, MT

Charles Sylvia Jr, DVM, MS, Covance Laboratories, Inc., Princeton, NJ

Address correspondence to Dr. Ryder (ryder1234@aol.com).

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Purpose. Infusate osmolarity, pH, and cytotoxicity were investigated as risk factors for midline catheter failure.

Methods. An experimental, randomized, controlled, blinded trial was conducted using an ovine model. Two 10-cm, 18-gauge single-lumen midline catheters were inserted into the cephalic veins of sheep. The animals were divided into 6 study arms and were administered solutions of vancomycin 4 mg/mL (a low-cytotoxicity infusate) or 10 mg/mL (a high-cytotoxicity infusate), doxycycline 1 mg/mL (an acidic infusate), or acyclovir 3.5 mg/mL (an alkaline infusate) and 0.9% sodium chloride injection; or 1 of 2 premixed Clinimix (amino acids in dextrose; Baxter International) products with respective osmolarities of 675 mOsm/L (a low-osmolarity infusate) and 930 mOsm/L (a mid-osmolarity infusate). Contralateral legs were infused with 0.9% sodium chloride injection for control purposes. Catheter failure was evaluated by assessment of adverse clinical symptoms (swelling, pain, leakage, and occlusion). A quantitative vessel injury score (VIS) was calculated by grading 4 histopathological features: inflammation, mural thrombus, necrosis, and perivascular reaction.

Results. Among 20 sheep included in the study, the overall catheter failure rate was 95% for test catheters (median time to failure, 7.5 days; range, 3–14 days), while 60% of the control catheters failed before or concurrently (median time to failure, 7 days; range, 4.5–14 days). Four of the 6 study arms (all but the Clinimix 675-mOsm/L and acyclovir 3.5-mg/mL arms) demonstrated an increase in mean VIS of ≥77% in test vs control legs ($P \leq 0.034$). Both pain and swelling occurred at higher rates in test vs control legs: 65% vs 10% and 70% vs 50%, respectively. The mean difference in rates of occlusive pericatheter mural thrombus between the test and control arms was statistically significant for the vancomycin 10-mg/mL ($P = 0.0476$), Clinimix 930-mOsm/L ($P = 0.0406$), and doxycycline 1-mg/mL ($P = 0.032$) arms.

Conclusion. Administration of infusates of varied pH, osmolarity, and cytotoxicity via midline catheter resulted in severe vascular injury and premature catheter failure; therefore, the tested infusates should not be infused via midline catheters.

Keywords: cytotoxicity, midline catheters, midline catheter failure, osmolarity, pH

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When introduced in the 1990s, midline and midclavicular catheters added attractive options for vascular access; however, their introduction occurred despite a lack of clinical efficacy and safety data. Soon, an increased occurrence of adverse thrombotic events, as well as a significant catheterization failure rate,[1] led to the abandonment of midclavicular tip positioning and dampened the use of midline catheters. To guide the appropriate use of peripheral and central vascular access devices (VADs), an algorithmic approach incorporating drug properties and therapy duration as key factors in

determining the optimal tip location was developed.[1,2]

Until 2016, the Infusion Nurses Society (INS) infusion therapy standard for VAD selection included pH and osmolarity criteria.[3] The 2011 INS standard recommended administering infusates with a pH of <5 or >9 and an osmolarity of >600 mOsm/L through a central venous catheter (CVC).[3] A revised INS standard published in 2016 removed the specific pH parameters and raised the osmolarity limitation for peripheral catheters—including midline catheters—from 600 mOsm/L to 900 mOsm/L in accordance with American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines.[4,5] The 2016 INS standard for VAD selection simply recommends considering infusate characteristics when selecting a device without providing further guidance.

Currently, 2 additional factors dramatically influence decisions in VAD selection: (1) the enactment of a financial penalty for central line–associated bloodstream infections (CLABSI); and (2) the expanded use of ultrasound and novel peripheral catheter technologies by an increasing number of clinicians and vascular access specialty teams. The changes in the INS standards and the adoption of advanced technologies enabled providers to explore using peripheral and midline devices for infusates typically administered through CVCs to avoid the CLABSI penalty, often without considering the impact of thrombotic adverse events on vessel health and preservation or the consequences of extravasation.

Several expanded variations of the original VAD selection algorithm have since been developed, most notably the Michigan Appropriateness Guide for Intravenous Catheters (MAGIC),[6-8] which recommends midline catheters for administration of peripherally compatible infusates for periods of ≤14 days; however, the MAGIC document provides limited evidence to support that recommended duration limit and lacks a clear definition of peripherally compatible drugs. There is a need to evaluate the use of midline catheters to administer infusates for extended periods.

KEY POINTS

- A preclinical study was conducted to investigate certain pharmacologic properties of infusates as risk factors for vascular injury and premature midline catheter failure in an ovine model.
- Infusates with varied pH, osmolarity, and nononcologic cytotoxicity resulted in severe vascular injury as well as premature midline catheter failure; therefore, they should not be infused via midlines.
- Consideration should be given to limiting midline catheter use to periods of <6 days to preserve vascular health.

The purpose of the randomized, controlled, blinded, preclinical trial described here was to investigate the role of infusate properties—pH, osmolarity, and nononcologic cytotoxicity (NOC)—as risk factors for midline catheter failure. Due to similarities in vasculature and hematologic factors between sheep and humans,[9-12] an ovine model was used to examine the effect of selected drugs on vessel health over a 14-day period, as recommended by the MAGIC document.[6] Macroscopic and histopathologic effects of upper and lower dose ranges on drug pH, osmolarity and NOC admixtures were compared to effects of isotonic 0.9% sodium chloride injection on vascular tissue injury.

Methods

Study subjects and setting. Twenty-four male and female crossbred (ie, black-faced and white-faced) sheep of similar size and weight were selected for the study. The sheep were selected based on good health and quarantined for 7 to 10 days prior to the study. The study was conducted at facilities of BioSurg, Inc., in Winters, CA. The study protocol was approved by the BioSurg institutional animal care and use committee. The study was sponsored by BD (Franklin Lakes, NJ), which had no control over study design and implementation, data analysis, or writing of the manuscript of this article.

Study design. The study was an experimental, randomized, controlled, blinded trial. Drug and control solutions were randomly assigned to be infused via a midline catheter placed in the left or right foreleg of each animal. The test drugs included 3 groups, each consisting of 2 study arms based on drug properties of interest: NOC, osmolarity, and pH. The following were administered separately in each of the 6 study arms: vancomycin 4 mg/mL (a low-NOC infusate, designated as V4); vancomycin 10 mg/mL (a high-NOC infusate, designated as V10); 2 solutions of Clinimix (amino acids in dextrose; Baxter International Inc., Deerfield, IL), ie, Clinimix 4.25/5, with an osmolarity of 675 mOsm/L (a low-osmolarity infusate, designated as C675), and Clinimix 4.25/10, with an osmolarity of 930 mOsm/L (a mid-osmolarity infusate, designated as C930); doxycycline 1-mg/mL solution (an acidic infusate); and acyclovir 350-mg solution (an alkaline infusate, designated as A350). The 930-mOsm/L Clinimix product was chosen because it is a commercially available premixed parenteral nutrition formulation with an osmolarity closest to the INS 2016 and ASPEN 2014 recommended osmolarity limit for peripheral vein infusions (900 mOsm/L).[4,5] Vancomycin was tested at the conventional concentrations of 4 and 10 mg/mL because no in vivo validation of its cytotoxic potential exists.[13] The control solution was 0.9% sodium chloride injection. Details regarding the test and control infusates are provided in Table 1.

The primary outcome was catheter failure, as determined according to 4 clinically relevant criteria, followed by a

Table 1. Test and Control Infusates

Drug Property	Drug[b]	Manufacturer	Test Infusates								Control Infusates[a]		
			Osmolarity (mOsm/mL)	pH[c]	Dose	Frequency	Base Vehicle	Vehicle Volume[d]	Infusion Rate (mL/h)	Infusion Period	IVF	Infusion Rate (mL/h)	pH[d]
Cytotoxicity													
Low	Vancomycin 4 mg/mL	Hospira	315[e]	3.89	1,000 mg	q 12 h	0.9% NaCl	270 mL	270	60 min	0.9% NaCl	270	6.62
High	Vancomycin 10 mg/mL	Hospira	328[e]	3.21	1,000 mg	q 12 h	0.9% NaCl	120 mL	120	60 min	0.9% NaCl	120	NM
pH													
Low	Acyclovir 3.5 mg/mL	NovaPlus	280[e]	11.06	350 mg	q 8 h	0.9% NaCl	107 mL	107	60 min	0.9% NaCl	107	6.89
High	Doxycycline 1 mg/mL	Premier Pro Rx	300[e]	2.12	100 mg	q 12 h	0.9% NaCl	120 mL	120	60 min	0.9% NaCl	120	NM
Osmolarity													
Mid	Clinimix 4.25/5	Baxter	675[f]	5.65	1,000 mL	q 24 h	NA	1,000 mL	125	8 h	0.9% NaCl	125	6.36
High	Clinimix 4.25/10	Baxter	930[f]	5.54	1,000 mL	q 24 h	NA	1,000 mL	125	8 h	0.9% NaCl	125	6.62

Abbreviations: IVF, intravenous fluid; NA, not applicable; NM, not measured
[a]Control infusates were administered at the same frequency and during the same infusion period as the corresponding drug.
[b]Final drug concentrations (for drug plus vehicle) were as follows: vancomycin 4 mg/mL, 3.7 mg/mL; vancomycin 10 mg/mL, 8.3 mg/mL; acyclovir 3.5 mg/mL, 3.3 mg/mL; and doxycycline 1 mg/mL, 0.83 mg/mL.
[c]Measured values.
[d]Drug volume plus base vehicle volume.
[e]Calculated values.
[f]Value obtained from product label.

histologic examination of vessel injury to quantify the role of drug properties as a risk factor for failure. The clinical criteria for catheter failure were as follows: (1) swelling, defined as upper leg circumference of ≥1 cm over baseline on 2 consecutive days; (2) pain (withdraw and/or jerking of leg on infusion or flushing or on palpation of the catheterized vein), defined as a pain score of 3 on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe) observed on 2 consecutive days, (3) observable leakage (fluid or drainage) from the catheter insertion site; and (4) unresolved catheter occlusion (inability to infuse and withdraw on 2 attempts).

The secondary outcome was the occurrence of an occlusive pericatheter mural thrombus (OPMT), defined as a large pericatheter sheath integrating with a mural thrombus and resulting in vessel occlusion. Additional measures included time to catheter failure (in days), vessel diameter, catheter:vessel ratio, blood flow rate, and time to sluggish or no blood return on evaluation of catheter patency prior to infusion.

Study procedures. Evidence-based practices were followed during catheter insertion, postinsertion care, and infusate administration.[4,14,15] Two 10-cm, 18-gauge single-lumen midline catheters (PowerGlide Pro RT Midline, BD, Franklin Lakes, NJ) were inserted into the cephalic veins of each sheep. Prior to catheter insertion, vessel circumference, area, and blood flow velocity at each insertion site and estimated catheter tip location were measured using color doppler (Sequoia 512, Siemens Medical Solutions, Mountain View, CA) with the animal standing, except for the study arm administered vancomycin 10-mg solution. For all groups, catheter size was determined by ultrasound (SiteRite 8, BD) and was chosen based on a catheter:vein ratio of 33% (not to exceed 45%).

Preoperatively each sheep was anesthetized, and its upper forelegs were sheared and scrubbed with 4% chlorhexidine solution for 2 minutes. The catheters were inserted in an operating room under maximum sterile barrier

precautions following application of ChloraPrep (BD). The catheter was flushed with 10 mL of NS0.9% sodium chloride injection. A needleless connector (Neutron, ICU Medical, Inc., San Clemente, CA) was connected to the catheter hub, and a protective antiseptic cap (SwabCap, ICU Medical) was placed on the connector. Catheters were sutured in place (2-0 Prolene, Johnson & Johnson, Bridgewater, NJ, and Ethicon Inc., Cincinnati, OH), and sterile surgical glue (SecurePortIV, Adhezion Biomedical LLC., Reading, PA) was applied to the insertion site before it was bandaged with a chlorhexidine foam disc (GuardIVa Bard Access Systems, Salt Lake City, UT), gauze, a self-adhesive wrap, and elastic adhesive tape. An analgesic (buprenorphine at a dose of 0.005–0.01 mg/kg) was administered to the sheep before recovery from anesthesia, and buprenorphine (0.01 mg/kg) was administered as needed, with sheep assessed by the veterinarian during the postoperative period for any pain or discomfort.

Infusions began on the first postoperative day, with test and control solutions administered concurrently. Upper leg circumference was measured at chest level before and after each infusion. Prior to infusion, catheters were aspirated for blood return and flushed with 10 mL of 0.9% sodium chloride injection via the push:pause technique. Catheters were flushed using the same technique after each infusion, locked with 0.9% sodium chloride injection, and a new SwabCap was applied. Disinfection of the needleless connector was performed using a scrubbing device containing 70% isopropyl alcohol (SiteScrub, BD) before each access and, on the catheter hub, via connector exchange. Clinimix solutions were administered using a 0.2-µ inline filter (B. Braun Medical Inc., Bethlehem, PA). Dressings were changed on postoperative days 3 and 8 or as required for drainage, disruption, or soilage; insertion sites were cleansed with alcohol, followed by ChloraPrep scrub, chlorhexidine foam disc placement, and rebandaging.

Study endpoint. Catheter failure (determined by pain, swelling, leakage, and/or occlusion) also served as an endpoint; the study concluded when a clinical criterion was met or the 14-day infusion period was completed. If a test catheter failed, then the corresponding control catheter was also removed. Upon reaching a study endpoint each sheep was euthanized, which included sedation with ketamine followed by administration of heparin i.v. (300 U/kg) and, finally, a commercially available euthanasia solution based on the recommendations of the American Veterinary Medical Association Panel of Euthanasia.

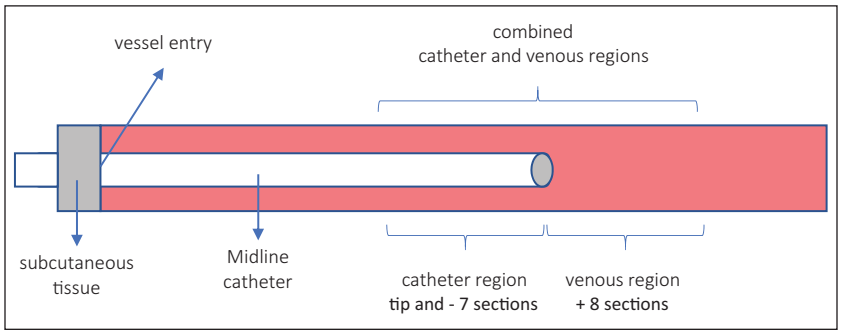
Histologic examination. *Gross necropsy.* The pathologist was blinded as to test and control leg and drug group. Both cephalic vein catheters were gravity perfused with up to 500 mL of 0.9% sodium chloride injection followed by 500 mL of 10% neutral buffered formalin (NBF). The vessel segment containing the catheter was excised en bloc, and the entire specimen was fixed in 10% NBF.

Gross evaluation and trimming. Beginning at the insertion site, serial "bread loaf" sections were made at ~3-mm intervals through the length of the catheter and for 10 cm beyond the tip (Figure 1). Tissues were trimmed into serial sections for histological processing. Cassettes were processed in graded alcohol, cleared in xylene, embedded in paraffin, sectioned in 4- to 6-µm increments, and stained with hematoxylin and eosin for microscopic evaluation.

Vessel injury score. There were 16 contiguous sections: 8 sections along the catheter, including the tip, and 8 sections in the venous region downstream of the tip (Figure 1). An aggregate measure of histopathology of each section was assessed as a vessel injury score (VIS) ranging from 0 to 16 (0, perfect health; 16, severe thrombophlebitis and tissue damage). The VIS was calculated as the sum of grades for the 4 histopathological features identified by the veterinary pathologist as the most relevant indicators of vessel injury: inflammation, thrombus, necrosis, and perivascular reaction (within a 5-mm radius around the vein). These features were graded semiquantitatively by the veterinary pathologist based on the following scale: 0, feature is absent; 1, presence is minimal; 2, mild; 3, moderate; and 4, severe.[16]

Statistical methods. The VIS values for control catheters were subtracted from the VIS values for the test catheter (for the same section), which provided 16 VIS differences for each sheep. VIS differences for each study arm were modeled by linear mixed-effect spatial models[17] with a random effect for animal and a fixed effect for region (ie, catheter or venous). Spatial dependence of VIS differences close to each other in the same vein were modeled by an AR(p) process. The spatial correlation structure was based on likelihood ratio tests, autocorrelation, and partial autocorrelation plots. AR(1)[18] spatial correlation structure was utilized in 5 study arms, while AR(2)[16] spatial correlation was employed for the C930 arm. The study was predicted to

Figure 1. Schematic of the 16 contiguous sections.



have 89% power to detect a difference in the VIS of 3.8 or more based on a power analysis of a pilot study of 4 animals subjected to infusions of vancomycin 4-mg/mL solution. The study was powered to the VIS, a quantitative measure that describes the reason for catheter failure. A study powered to the binary outcome of catheter failure (failed or not) would have less power to detect the real differences between study arms.

The percentage of sections associated with an OPMT for the control leg was subtracted from the percentage for the test leg for each animal. These differences were analyzed by analysis of variance (ANOVA) with a factor for study arm.

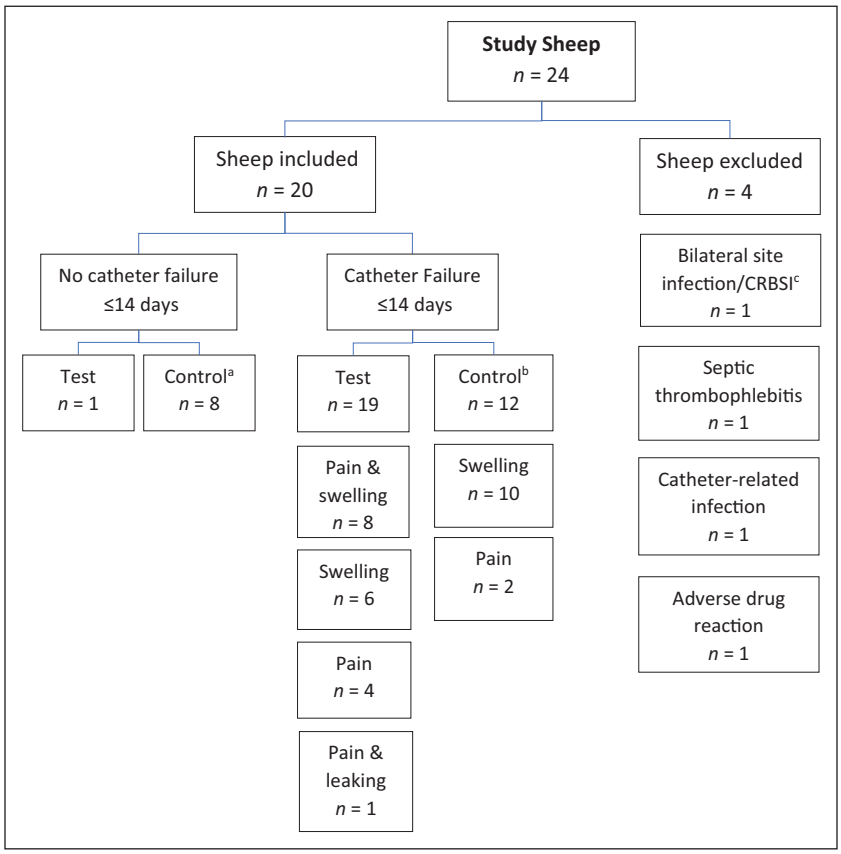
Individual value, residual, and normal probability plots were used to detect outliers for all models and to check the normality and homogeneity of variance assumptions of the spatial and ANOVA models. The single-step method was used to maintain a 95% family-wise confidence level for each analysis separately. All analyses were performed using R v3.4.2[19] packages nlme[17] and multcomp.[20]

Results

Subjects. Of the 24 animals initially enrolled in the study, 4 were excluded from the analyses. Test and control catheters (20 each) in 20 sheep were analyzed (Figure 2).

Catheter failure. The overall failure rate was 95% in the test catheters (median time to failure, 7.5 days; range, 3–14 days). Twelve (60%) of the control catheters failed before or at the same time as the test catheters (median, 7 days; range, 4.5–14 days); 8 (40%) of the control catheters were removed without failure when their corresponding test catheter failed. One test animal survived 14 days with no catheter failure, while 19 sheep experienced failure before the 14-day period, 3 of which had failures on day 14. Three of 4 clinically relevant symptoms of catheter failure were observed: swelling, pain, and leakage; there were no unresolved catheter occlusions. More than 1 symptom occurred in 9 (45%) of the 20 test legs (pain and swelling [8 of 9 legs] and pain and leakage [1 of 9 legs]). Ten (50%) of control-leg catheterizations failed due to swelling, and 2 (10%) due to pain. Pain and swelling occurred more frequently in test vs control legs (65% vs 10% and 70% vs 50%, respectively).

Figure 2. Subject profile chart of all enrolled sheep. CRBSI indicates catheter-related bloodstream infection.



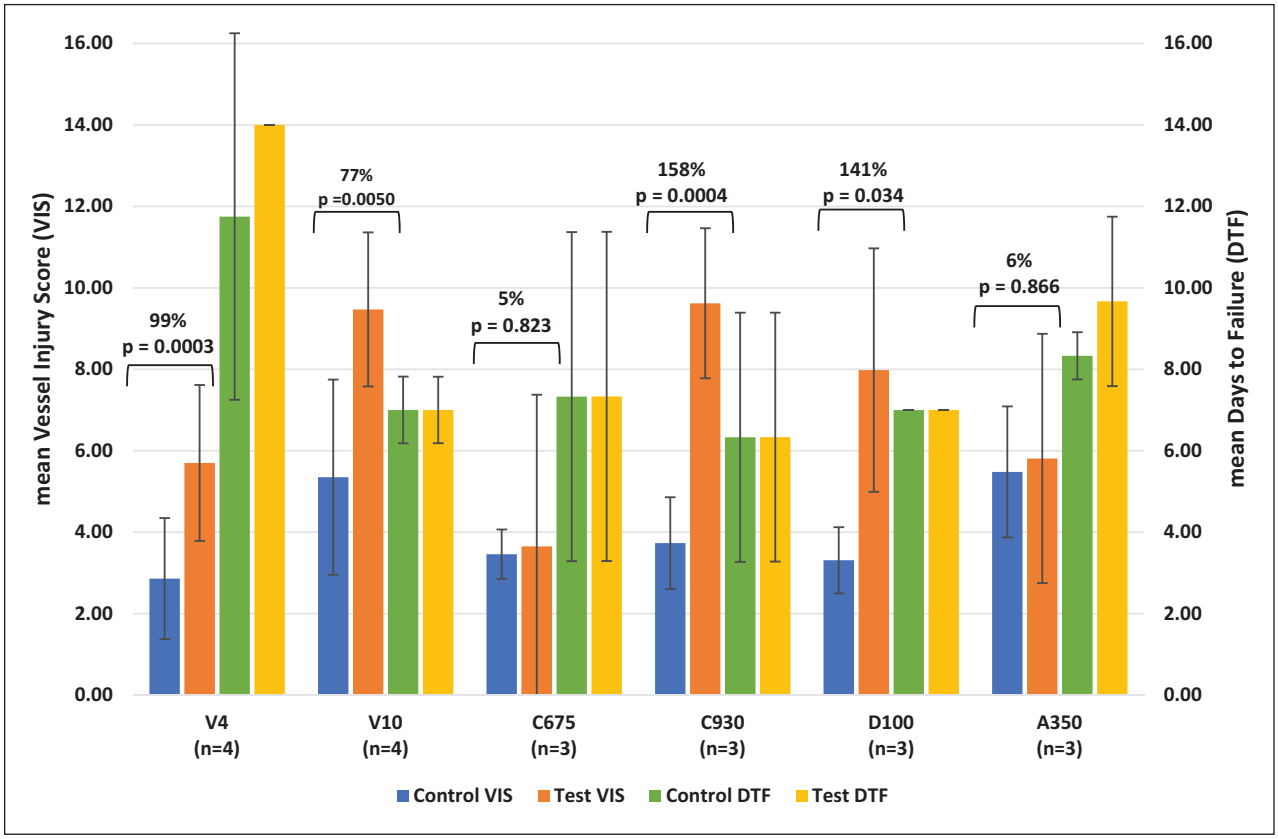
[a]These 8 control catheters were "right censored," ie, did not have failure at the time when test catheters were removed due to failure (if a test catheter failed, then the corresponding control catheter was also removed). [b]Catheter failure was observed in 12 control catheters at same time or before the test catheter.

Vessel injury score. Differences in VIS for each group are shown in Figure 3. Four of the 6 arms (all except the C675 and A350 arms) demonstrated an increase in mean VIS values of ≥77% in test legs relative to controls ($P \leq 0.034$). Catheter failures may be explained by the test catheters having worse (ie, higher) VIS values on average compared to the concurrent controls in every study arm.

VIS values among control catheters were not statistically significantly different ($P = 0.252$). However, combined VIS values were markedly worse (ie, higher) for the controls in the high-NOC group vs low-NOC group (V10 vs V4) and for the alkaline solution vs the acidic solution (A350 vs D100) (Figure 3).

Thrombotic events. The 3 observed clinical symptoms were all associated with thrombotic events, including mural thrombus adhered to the vessel wall (Figure 4; panels C, E, and G); OPMT (Figure 4, panels D and F), and nonadherent pericatheter sheath (Figure 4, panel B). OPMT was observed in 50% of test catheters and 5% of control catheters. In every study arm, the test catheters were associated with OPMT,

Figure 3. Mean vessel injury score (VIS) and mean days to failure (DTF) values for the test and control legs by arms of study. The percent increase in the VIS of the test legs vs control legs, as well as the associated *P* value, is indicated for each of the 6 arms of the study. Error bars indicate SD values.[a]



[a]Equal values for control and test DTF were observed for V10, C675, C930, D100 test groups since corresponding control catheter was removed when a test catheter failed; 8 control catheters were "right censored" (ie, did not fail by the time the treated catheter failed).

as compared to only 1 instance of OPMT involving a control catheter. The mean rates of OPMT between test and control arms were statistically significantly different for the V10 (P = 0.048), C930 (P = 0.041), and D100 groups (P = 0.032) but not for the V4, C675 or A350 groups (Figure 5). Occlusive mural thrombus also occurred in the venous region proximal to the catheter tip in 40% of the test and 20% of control legs (Table 3). The rate and severity of thrombotic events were greater in the test legs than in the control legs (Table 3). Thrombotic events were more extensive when pain and swelling occurred together than when pain or swelling occurred alone (Table 3).

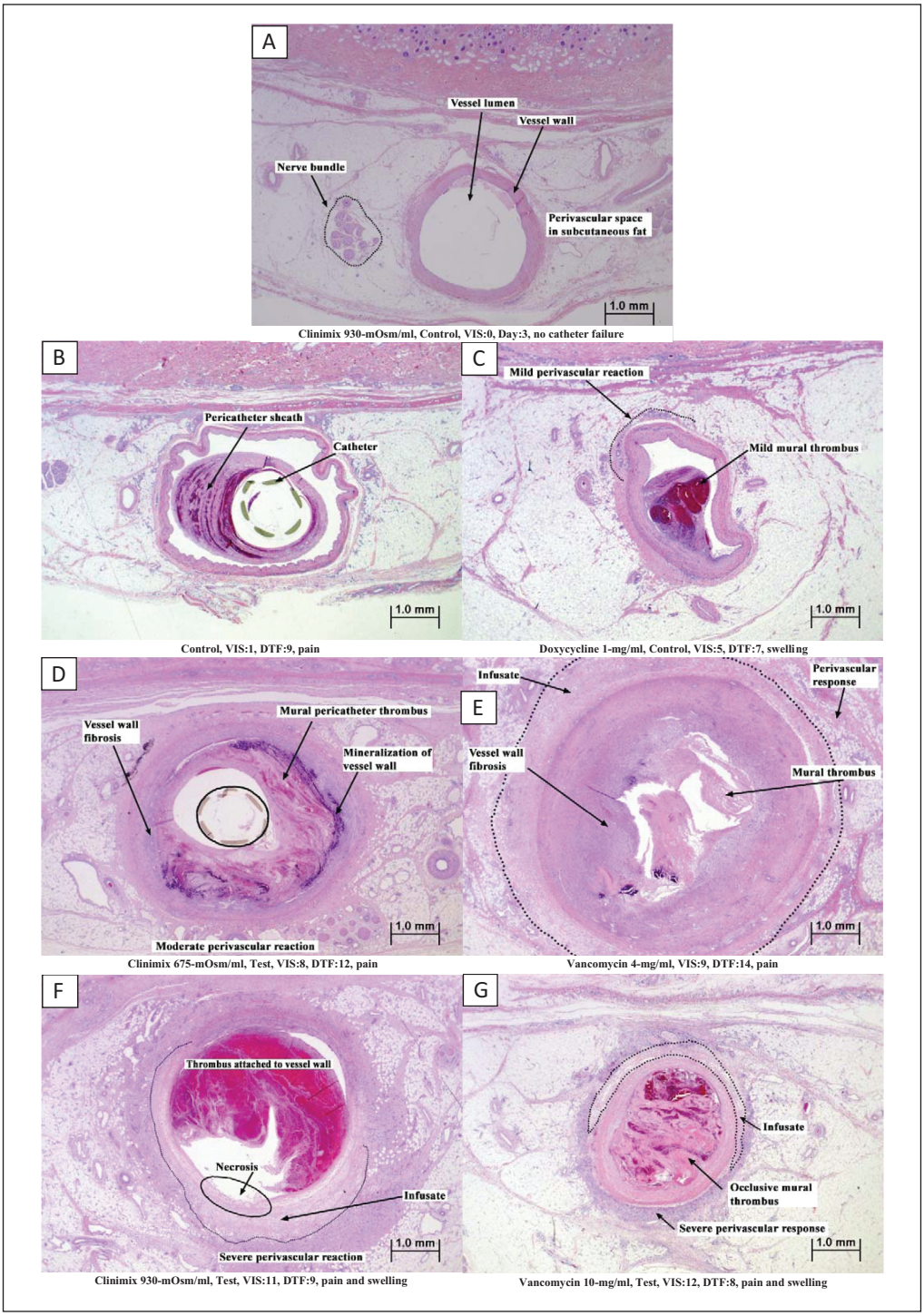
Additional measures. Comparison of mean vessel diameters and catheter:vein ratios for test and control legs are listed in Table 2. There were no statistically significant differences in either vein diameter or catheter:vein ratio between the test and control legs, within or between drug groups, or between locations (insertion site vs tip). Mean preinsertion blood flow measures at the insertion site and the tip for test and control legs are reported in Table 2.

Blood return. Each catheter was evaluated for blood return followed by a flush before infusion each day. Blood return was absent in 42% of test catheter attempts and 32% of control catheter attempts. Mean time to sluggish blood return was 1.5 days in the test groups and 2.5 days in control groups, and mean time to no blood return was 3.8 days for both groups. Fibrin sheath to the tip or beyond was observed in all but 1 test catheter with loss of blood return and all but 4 of the control catheters. All vessels had mural thrombus beyond the tip.

Discussion

The trial investigated the impact on sheep vasculature when exposed to drug therapies that were outside the projected range of human tolerance for pH, osmolarity, and cellular toxicity for peripheral veins. We selected infusates with extreme pH (2 and 11) compared to the safe range of 5 to 9 based on aggregate population data from drug trials.[3] Furthermore, we looked at the effect of standardized parenteral nutrition solutions with osmolarities of 675 and 930

Figure 4. Histology images showing examples of observed histopathological features in control and test legs. Panel A: Normal venous histology. Panel B: Moderate sized nonadherent pericatheter sheath comprised of fibrin, platelets, and red blood cells. Panel C: Mural thrombus adherent to the vessel wall with mild intimal hyperplasia and perivascular reaction. Panel D: Large adherent pericatheter mural thrombus with vessel wall mineralization and fibrosis. Panel E: Chronic mural thrombus organization with marked vessel stenosis and perivascular extravasation. Panel F: Partially occlusive pericatheter mural thrombus with vessel necrosis and severe perivascular reaction from extravasation. Panel G: Occlusive mural thrombosis proximal to catheter tip and severe perivascular reaction from extravasation.



mOsm/L, which are above the previously recommended osmolarity range of <600 mOsm/L.[3,5] The literature regarding associations between endothelial damage and osmolarity and/or pH is mostly limited to animal data involving parenteral nutrition, which is a complex solution.[21-23] Without sufficient data, these results may not be transferable to single-drug therapies. The literature is also scarce regarding the impact of direct cellular toxicity from nonantineoplastic drugs. Over 20 years ago, a limited body of work was performed to evaluate how several drugs, including vancomycin, altered in vitro endothelial intracellular processes.[24,25] Vancomycin was shown to be well tolerated in concentrations of 2 to 5 mg/mL, but higher concentrations (eg, 10 mg/mL) caused endothelial cell damage. In 2015, Drouet et al[9] showed that vancomycin in concentrations greater than 2.5 mg/mL resulted a significant increase in vascular endothelial cell death, with a median lethal dose of 5 mg/mL. However, these studies did not consider the duration of exposure, which is a key factor in infusion therapy.

Kuwahara's rabbit model was the only preclinical model investigating the effect of pH and osmolarity on small peripheral veins.[21-23] We used the sheep model since sheep vasculature and hematologic factors are comparable to those in humans,[10,12,26] and they are adaptable to long-term infusions. The model allowed us to investigate the vessel response through direct histological observation of vessel injury that would not be detectable by clinical assessment. The histologic VIS, which represents the combined vessel damage and thrombosis of the catheter and venous regions, was used to measure vessel injury. As the VIS increases, the risk of irreversible damage increases, which may preclude recatheterization of the vessel.

The histopathological examination demonstrated significant differences in the VIS between the control and test legs for the V4, V10, C930, and D100 infusates. The C675 and A350 infusates produced extensive damage by 7 days on average, with no statistically significant difference in VIS between test and control legs. However, all test infusates caused clinically significant vascular damage.

Hemodilution of intravenous drugs is dependent on blood volume and flow velocity. Blood flow in vessels of the axillary region is considered sufficient to provide adequate dilution without vessel injury. In our study, the mean diameter of veins at the catheter tip was 4.5 mm, which is analogous to the mean diameter in humans,[27-29] and the mean preinsertion blood flow was 20 mL/min. According to Nifong et al,[30] introduction of an 18-gauge catheter would reduce the rate to ~11 mL/min, dramatically increasing the exposure of

Figure 5. Percentage of the histological sections associated with an occlusive pericatheter mural thrombus (OPMT) for the test and control legs in each of the 6 arms of the study (each vein had 16 sections). Error bars indicate SD values. The percent increases in the percentage of the vein with OPMT of the test legs vs control legs, as well as the associated *P* values, are indicated for each of the 6 arms of the study. NC indicates not calculable for the D100 arm due to 0% of the control sections being associated with OPMT.

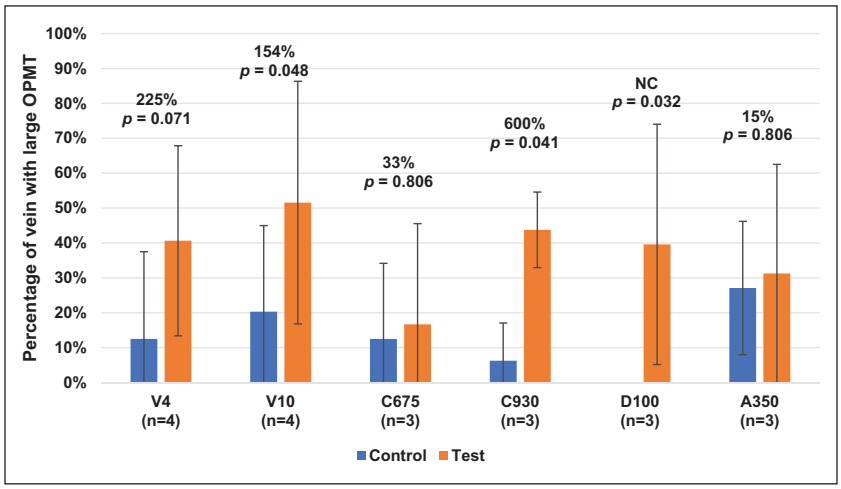


Table 2. Descriptive Data for Vessel Diameter, Catheter:Vein Ratio, and Blood Flow in Test and Control Arms, by Measurement Site

	Test (*n* = 20)		Control (*n* = 20)	
Variable	**Insertion Site**	**Tip**	**Insertion Site**	**Tip**
Vessel diameter, mean (range), mm	4.3 (4.1-4.7)	4.6 (4.2-4.9)	4.3 (3.9-4.9)	4.5 (4.2-4.8)
Catheter:vein ratio, mean (range) % vein occupancy	30.4 (28.0-33.3)	28.8 (26.7-31.0)	30.6 (28.7-33.8)	27.3 (27.3-31.0)
Preinsertion blood flow, mL/min	18.5	19.6	22.8	19.6

Table 3. Symptoms and Thrombotic Events by Study Arm

Outcome	Test (*n* = 20)	Control (*n* = 20)
Endpoint criteria, %		
Pain (alone)	20	10
Swelling (alone)	30	50
Pain and swelling	40	0
Leakage at catheter site	0	0
Leakage and pain	5	0
Catheter occlusion	0	0
Pericatheter sheath, %	100	85
Pericatheter sheath before catheter tip, %	15	30
Pericatheter sheath to catheter tip, %	60	50
Pericatheter sheath beyond catheter tip, %	25	5
Occlusive pericatheter mural thrombosis (catheter region), %	50	5
Occlusive mural thrombus (venous region), %	40	20
Mural thrombus proximal to tip	100	100
Time to sluggish flush, mean, d	4.3	3.5
Time to sluggish blood return, mean, d	1.5	2.5
Time to no blood return, mean, d	4.3	3.5

the drug to the endothelium. Impaired venous valve function in the catheter region facilitates retrograde flow of the infusate, which in turn exacerbates damage to the vessel. This might explain the higher rate of vascular injury and OPMT in the test legs. Catheter failure was observed in all but 1 of the test catheters in the 14-day period. Histopathologic findings confirmed vessel injury at a median of 7.5 days in all test catheters and 8 days in 60% of control catheters. Catheter failure occurred at about 7 days for infusates V10, C930, C675, and D100, compared to 10 days for infusate A350 and 14 days for infusate V4. Twelve (60%) control catheters failed the same day as the test catheter, which suggests that catheterization in peripheral vessels, in and of itself, may result in failure as a function of time. This may account for reports in the literature that show higher rates of thrombosis and thrombotic symptoms in midline catheters compared to PICCs or CVCs.[31-36] However, recent reports indicate thrombotic events may also be associated with devices in distant locations, which might explain the high catheter failure rate observed in the control legs.[33,37-39]

Symptoms of leaking, pain, and swelling are not complications in and of themselves, as is typically reported in the literature[31,32,40,41]; they are signs of vessel damage and thrombosis, as evidenced by histopathological examination. Unlike with use of short peripheral i.v. catheters in the forearm, extravasations in the upper arm are difficult to detect until symptoms are severe and vessel damage is intractable. The poor outcomes observed in our study occurred despite the use of optimal catheter:vein ratios and careful adherence to standards of care for insertion and device maintenance. Outcomes would likely be worse if optimal standards were not followed.

The pharmacologic properties of an infusate must be considered as a risk factor for vascular injury and premature midline catheter failure. Our findings verify that pH is an independent risk factor that influences vessel health and may contribute to harmful outcomes. The previously established pH range of 5 to 9 is likely the safest option when all exacerbating factors for thrombophlebitis are considered. The results are in agreement with those of prior studies addressing the osmolarity of parenteral nutrition and demonstrate that frequency and severity of thrombophlebitis increase significantly as the osmolarity exceeds 600 mOsm/L.[42] Time to failure of the cytotoxic V4 and V10 infusates differed, but both resulted in significant vessel injury and occlusive thrombosis. The difference in severity of vessel injury between the doses of vancomycin appeared to be dose dependent. The best practice is to limit peripheral administration of vancomycin 4-mg solution to a short peripheral catheter for 72 to 96 hours while awaiting blood culture results and conducting careful monitoring.

There were a number of study limitations. First, since the animals were selected based on good health, they responded to both the presence of a catheter and the infusions without exacerbations produced by illness. However, midline catheters are generally placed in sick patients, which may lead to more severe physiological responses due to thrombogenicity risk factors. Second, our research might have overstated the time to failure, as the study parameters required more than 1 day of observable symptoms before subject removal from the study. Third, using the contralateral leg of the same subject for the control catheter may have produced a negative bias in controls due to administration of the test infusion via the contralateral leg. Initially, this was not seen as an issue; however, recent reports indicate an association of a venous thrombotic event with devices in distant locations.[33,37-39] The ramifications of these limitations are not clear but may explain in part the unanticipated degree of severity of injury observed in control veins.

Conclusion

Drug properties including pH, osmolarity, and cytotoxic potential, as well as the duration of therapy and the choice of the most appropriate vascular access device, remain relevant in preventing vessel injury and patient harm. Clinical symptoms of thrombotic events and extravasation and/or infiltration are significant indicators of potential irreversible venous damage. Infusates with varied pH, osmolarity, and cytotoxicity tested in this study resulted in severe vascular injury and premature midline catheter failure; therefore, they should not be infused via midline catheters. The fact that most midline catheters failed within 7 days and that the longest duration was 14 days raises questions about the recommendation of midline catheter use for up to 14 days. Consideration should be given to limiting midline catheter use to a duration of <6 days to preserve vascular health.

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Previous affiliations

At the time of the study Dr. Sylvia was affiliated with Biosurg, Inc., Winters, CA.

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