

Experimental study on the hemostatic effect of cyanoacrylate intended for catheter securement

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Abstract

Purpose: The use of cyanoacrylate for intravenous catheter securement is of interest to clinicians and patients, because of the superior adhesive strength and hemostatic effect of cyanoacrylate compared to current securement devices. The purpose of this study is to use novel in vitro and in vivo testing methods to analyze the hemostatic effect of a catheter securement cyanoacrylate (cyanoacrylate).

Methods: An unprecedented in vitro method was performed to determine the effects of a cyanoacrylate on a customized modified activated clotting time assay and blood flow inhibition assay by exposing blood or plasma to either one or three drops of cyanoacrylate. For the in vivo testing, full-thickness incisions were made on swine, and the bleeding was scored prior to treatment and at 3, 6, 9, and 12 min after treatment.

Results: The cyanoacrylate rapidly achieved hemostasis in the presence of anticoagulated whole blood, platelet-poor plasma, and non-anticoagulated whole blood, in vitro. The cyanoacrylate achieved hemostasis 12-fold faster than thromboplastin in the modified activated clotting time assay. The cyanoacrylate does not alter normal blood clotting, as measured by prothrombin time. In vivo, the bleeding score of cyanoacrylate prior to treatment and at 3, 6, 9, and 12 min after treatment were 2.3 ± 1.0 , 0.3 ± 0.5 , 0.2 ± 0.5 , 0.2 ± 0.4 , and 0.2 ± 0.4 , respectively.

Conclusion: This study indicates that cyanoacrylate demonstrates a potent mechanical hemostatic effect and cyanoacrylate in the presence of anticoagulated whole blood has an activated clotting time that is 12 times quicker than thromboplastin. The cyanoacrylate was found to be significantly equivalent to two known hemostatic agents, in vivo.

Keywords

Adhesive, catheter, cyanoacrylate, hemostasis, medical device

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Introduction

The use of cyanoacrylate to secure intravenous catheters to the skin is a recent topic of discussion among health care professionals trying to reduce risks commonly presented when using intravenous catheters.^{1,2}

Cyanoacrylate used as a securement device is a scarcely explored area compared to the research on conventional catheter securement products. While cyanoacrylate has been shown to demonstrate stronger, more consistent securement of intravenous catheters compared to the currently used products,³ it is equally important to investigate the hemostatic effects of cyanoacrylate. Hemostasis is the process in which blood flow is arrested to prevent bleeding; it consists of three major steps which are vasoconstriction, platelet

plug formation, and coagulation.⁴ Because the cannulation process produces a small hole in the skin and vein of the patient, a securement device that has the ability to assist with hemostasis and prevention of hematomas is desired.⁵ Cyanoacrylate has the ability to stop bleeding from the insertion site, resulting in a safer catheter dwell period

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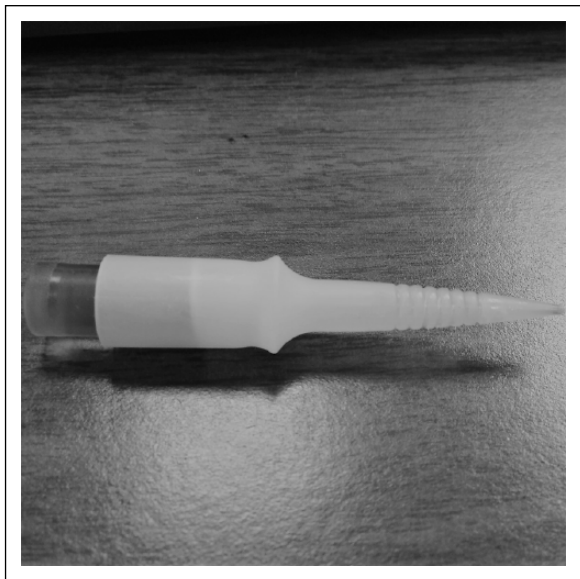


Figure 1. Cyanoacrylate.¹⁴

which could potentially lead to less catheter-related bloodstream infections (CRBSIs) and hematomas compared to conventional securement devices, yet the research regarding its hemostatic effect is limited.

Davis et al.⁶ studied the effect of octyl cyanoacrylate (OCA) on partial-thickness wounds in a porcine model, noting a hemostatic effect upon application. A second study clinically tested an OCA liquid bandage, which proved to be twice as effective in controlling bleeding over the control bandage.⁷ While Eaglestein and colleagues^{6,7} demonstrate that cyanoacrylate has the ability to act as a hemostatic agent, they are limited because only one single point of hemostasis assessment was obtained, and the interaction between cyanoacrylate and wet/bleeding wounds was not observed because the wounds were dried prior to cyanoacrylate application. Both Lin⁸ and Singer et al.⁹ reported hemostatic effects when applying multiple layers of cyanoacrylate on wounds. Singer et al.¹⁰ conducted another study where a liquid dressing placed on partial-thickness wounds was also effective in achieving hemostasis. A major limitation in the aforementioned studies is that >1 mL of adhesive was used to achieve hemostasis.^{9,10} Besides OCA, n-butyl-2-cyanoacrylate was used in combination with sutures and ethyl-2-cyanoacrylate was used in combination with tourniquets to control bleeding in two other studies.^{11,12} A major limitation in the previously conducted studies is that multiple layers of cyanoacrylate, in some cases >1 mL, were used to stop the bleeding.

The hemostatic effect of cyanoacrylate has been previously studied, but to our knowledge the hemostatic effects of a cyanoacrylate product intended to secure catheters using 0.15 mL or less has not been studied.⁶⁻¹³ The purpose

of this study is to demonstrate, through novel *in vitro* and *in vivo* experimental methods, the hemostatic properties of the first catheter securement adhesive (cyanoacrylate) approved by the Food and Drug Administration (FDA).

Methods

An experiment was conducted, *in vitro*, to determine the mechanical hemostatic properties of cyanoacrylate¹⁴ by means of customized modified activated clotting time (mACT) and blood flow inhibition (BFI) assays. These assays were conducted by a third party laboratory. The test article, a cyanoacrylate,¹⁴ can be seen in Figure 1. To activate the cyanoacrylate, the ampoule was pressed inward while the tip was facing upright. Once activated, the applicator was inverted so that the tip was facing downward allowing the adhesive to flow to the tip and promoting the release of individual drops. To study the mechanical hemostatic properties while in contact with blood or plasma, two test article groups (one and three drops of cyanoacrylate) were studied, with a new applicator being used for each test. There was a negative control (saline) and a no-treatment control, totaling four test groups. Thromboplastin was used as a positive chemical control in the mACT when anticoagulated whole blood was tested. Each test group was evaluated with citrated whole blood (diluted 1:1 with saline), platelet-poor plasma (PPP; prepared via centrifugation of citrated whole blood at 2500 × g for 20 min at 21°C), and non-anticoagulated whole blood (diluted 1:1 with saline), each from four healthy donors. Anticoagulated whole blood was used to determine if cyanoacrylate can stop blood that cannot clot. PPP was used to determine the cyanoacrylate's effect in a cell-free system. Non-anticoagulated whole blood was used to determine the cyanoacrylate's effect in physiological conditions.

A Diagnostica Stago[®] ST4 (clotting analyzer) was used on blood samples collected into sodium citrate anticoagulant or non-additive vacutainer tubes to evaluate the effects of cyanoacrylate on mACT assay. An amount of 75 μL of diluted whole blood or neat PPP was added to each well containing a Stago mixing ball. A prothrombin time (PT) test with normal pooled plasma and Neoplastine CI Plus reagent was performed on each day of testing as a control standard. For testing cyanoacrylate, the PT test was selected on the Stago ST4, and inside the incubation wells a test strip was placed for ~3 min before being transferred to the test wells to ensure that all components were at 37°C. The test was initiated when cyanoacrylate was deployed and had a maximum time limit of 180 s. Diluted whole blood was also exposed to Neoplastine CI plus reagent to provide a comparison with a known chemical hemostatic agent (thromboplastin) in this customized mACT assay. These tests were performed in duplicate with the results being presented as the amount of time (seconds)

it took to achieve hemostasis with cyanoacrylate in the presence of whole blood or blood product.

To evaluate the effects of cyanoacrylate on customized BFI assay, three sodium citrate vacutainer tubes or one non-additive tube was used to collect blood. Two out of the three sodium citrate tubes were used to prepare PPP. The BFI assay was conducted through a perfusion system with a peristaltic pump (Instech)-driven flow. The perfusion system was assembled by installing a peristaltic tubing around the pump rotor with a 4-in C-flex tubing (0.062 in ID) attached to the proximal and distal nodes of the tubing. Furthermore, the proximal and distal ends of the tubing each contained a 1.5-mL Eppendorf tube that was used as the blood source and for blood collection during the assay, respectively. The pump was set to 0.25 mL/min flow rate and 1 mL of citrated diluted whole blood, non-anticoagulated whole blood, or PPP was perfused through the tubing until the blood reached the distal end. Cyanoacrylate was applied to the tubing tip as the blood reached the distal end of the tubing. Once the blood flow stopped for ~3 s, mechanical hemostasis was considered to be achieved. The tubing was then removed and the total amount of collected blood was determined by subtracting the weight of the blank Eppendorf tube (1 g) from the weight of the tube containing the collected blood. All tests were performed in duplicate and the results are presented in grams. The statistical analysis was performed on GraphPad Prism software version 6.0 and the results were analyzed by one-way analysis of variance. A value of $p < 0.05$ indicated statistically significant differences.

During the mACT assay, if the blood flow is impeded slowing the movement the instruments will then recognize the clot formation detecting hemostasis. During the BFI assay, if the collection tube is less in weight, then the test article successfully inhibited the blood flow thus detecting hemostasis.

A comparison study, *in vivo*, was conducted to show the hemostatic effect of cyanoacrylate in direct comparison to known hemostatic agents Gelfoam Powder (HA1) and Kaltostat (HA2) and to a sham control (SC; no treatment). Each agent was applied to dermal incisions in heparinized swine. The *in vivo* swine study was conducted by a third party laboratory and conformed to the "Guide for the Care and Use of Laboratory Animals" with approval by the Institutional Animal Care and Use Committee (IACUC) prior to conducting this animal study. Two, Yorkshire cross, female swine 88–89 kg in weight were used to create 120 linear and full-thickness incisions (through the entire depth of the skin). Each incision was treated with either cyanoacrylate, HA1, HA2, or with the SC, for which a hemostasis score was determined. The swine were induced under general anesthesia, and the hair surrounding the incision site was removed. In order to achieve adequate blood flow, fluids were administered to maintain or increase systolic blood pressure, and heparin

was administered and monitored by testing the activated clotting time (ACT) levels. Cyanoacrylate was activated as previously mentioned, and once enough adhesive was dispensed (five drops maximum per incision), it was spread into a thin layer using the applicator tip. The comparative controls of known hemostatic devices, HA1 and HA2, were prepared and applied per each product's instructions for use.^{15,16} There were 30 sites located on each side of the back for each pig (120 in total). The incisions were in three rows of 10 outlined with a marker; each full-thickness incision was between 7 and 10 mm in length. Of the 60 incision sites per animal, cyanoacrylate, HA1, HA2, and the SC, each treated 15 incisions. The treatments that each incision site received were rotated in a repeating order until all incisions were treated. When using the SC, no treatment was applied after an incision was made, and an initial score for blood flow was recorded. For the other three articles, after the incision was made and an initial score for blood flow was recorded, the test article was applied. After application or no application in the case of the SC, a 30-s rest time began for all sites. Following this rest time, the sites were scored for blood flow at 3, 6, 9, and 12 min. At the end of 12 min, dry gauze was used to stop any additional bleeding, if present.

If the blood flow from the incisions made *in vivo* decreases upon application of the test article compared to the control, then hemostatic effects are considered to be demonstrated. The primary endpoint for the *in vivo* and *in vitro* study was the detection of hemostasis.

The statistical analysis was performed by screening the data, and a value of $p < 0.05$ represented statistically significant differences. Normally distributed data with equal variance were considered parametric and were evaluated using an unpaired t test. If the data were not parametric, then they were evaluated by the Mann-Whitney rank-sum test.

Results

In vitro, one and three drops of cyanoacrylate in the presence of anticoagulated whole blood took an average time of 2.00 ± 0.52 and 1.99 ± 0.80 s, respectively, to achieve hemostasis, while a known hemostatic agent, thromboplastin, took an average time of 25.10 ± 3.12 s. Cyanoacrylate achieved mechanical hemostasis 12 times faster than thromboplastin in anticoagulated whole blood, which was significantly quicker. One and three drops of cyanoacrylate in the presence of PPP took an average time of 2.14 ± 0.86 and 2.33 ± 1.55 s, respectively, to achieve hemostasis. One drop and three drops of cyanoacrylate in the presence of non-anticoagulated whole blood took an average time of 3.24 ± 2.19 and 2.24 ± 1.01 s, respectively, to achieve hemostasis. Saline and no treatment took >180 s to achieve hemostasis in the presence of anticoagulated whole blood, PPP, and non-anticoagulated whole blood. In all three blood

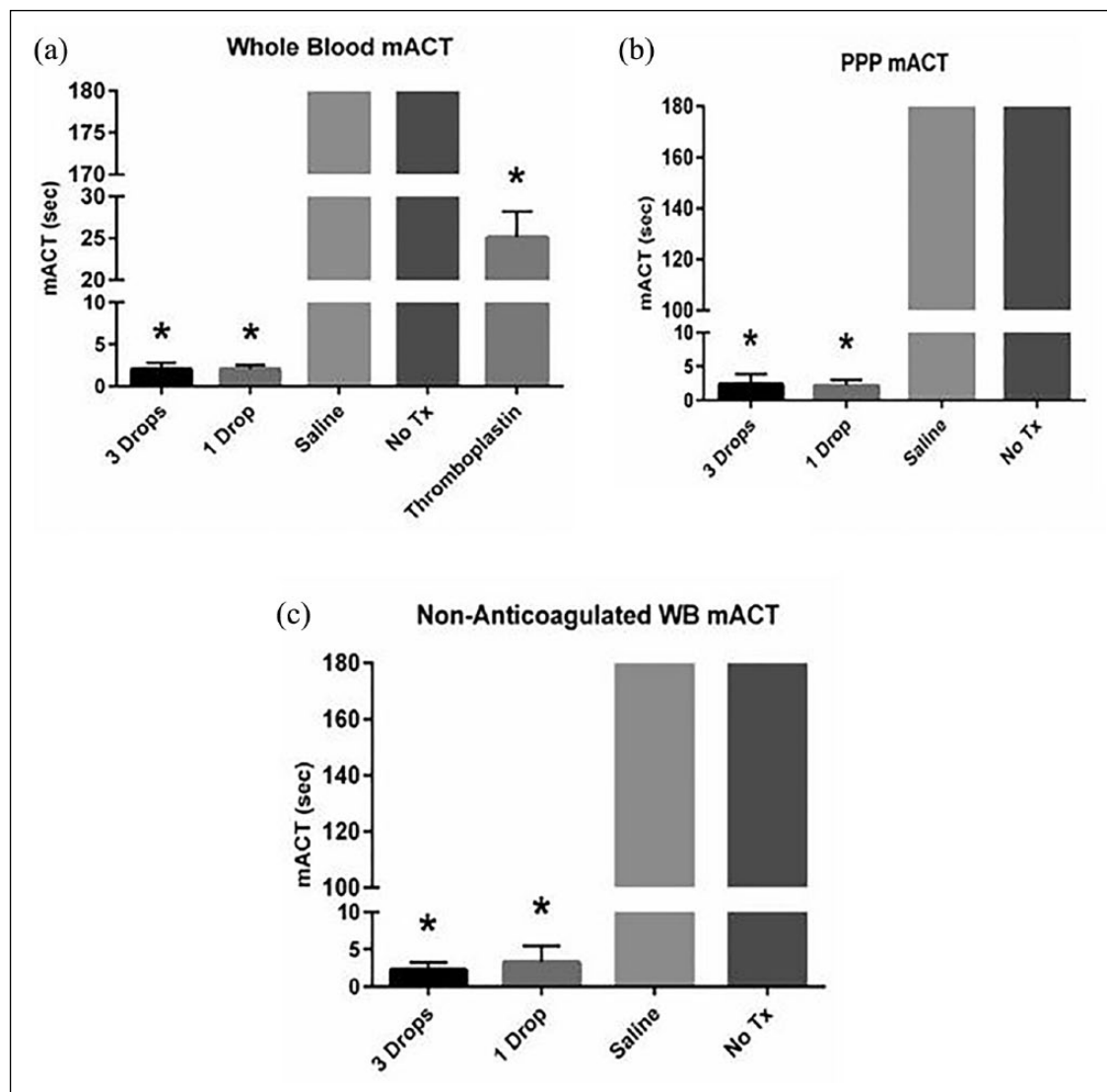


Figure 2. mACT assay on (a) anticoagulated whole blood, (b) PPP, and (c) non-anticoagulated whole blood (3 Drops or 1 Drop—drops of cyanoacrylate, saline; No Tx—no treatment, Thromboplastin. Asterisk indicates statistically significant difference compared to the No Tx group ($p < 0.05$; $n = 8$)).

media, both one and three drops of cyanoacrylate were statistically significantly more effective in achieving mechanical hemostasis compared to the no-treatment group, while saline treatment did not demonstrate any statistical significance. All results from this customized mACT assay are demonstrated in Figure 2.

The BFI assay was conducted and the blood collection weight was recorded for all blood test substances. The average weights of citrate anticoagulated whole blood collection contents after coming in contact with one and three drops of cyanoacrylate are 0.15 ± 0.04 and 0.13 ± 0.04 g, respectively. The average weights of citrate anticoagulated whole blood collection contents after coming in contact with saline and no treatment are 1.10 ± 0.04 and 1.04 ± 0.03 g, respectively. The average weights of PPP collection

contents after coming in contact with one and three drops of cyanoacrylate are 0.13 ± 0.04 and 0.13 ± 0.05 g. The average weights of PPP collection contents after coming in contact with saline and no treatment are 1.12 ± 0.04 and 1.07 ± 0.03 g, respectively. The average weights of non-anticoagulated whole blood collection contents after coming in contact with one and three drops of cyanoacrylate are 0.13 ± 0.03 and 0.12 ± 0.01 g, respectively. The average weights of non-anticoagulated whole blood collection contents after coming in contact with saline and no treatment are 1.10 ± 0.03 and 1.06 ± 0.05 g, respectively. Both one and three drops of cyanoacrylate were statistically significantly more effective compared to the no-treatment group. Saline accounted for additional weight compared to the no-treatment group, making it statistically significantly equal

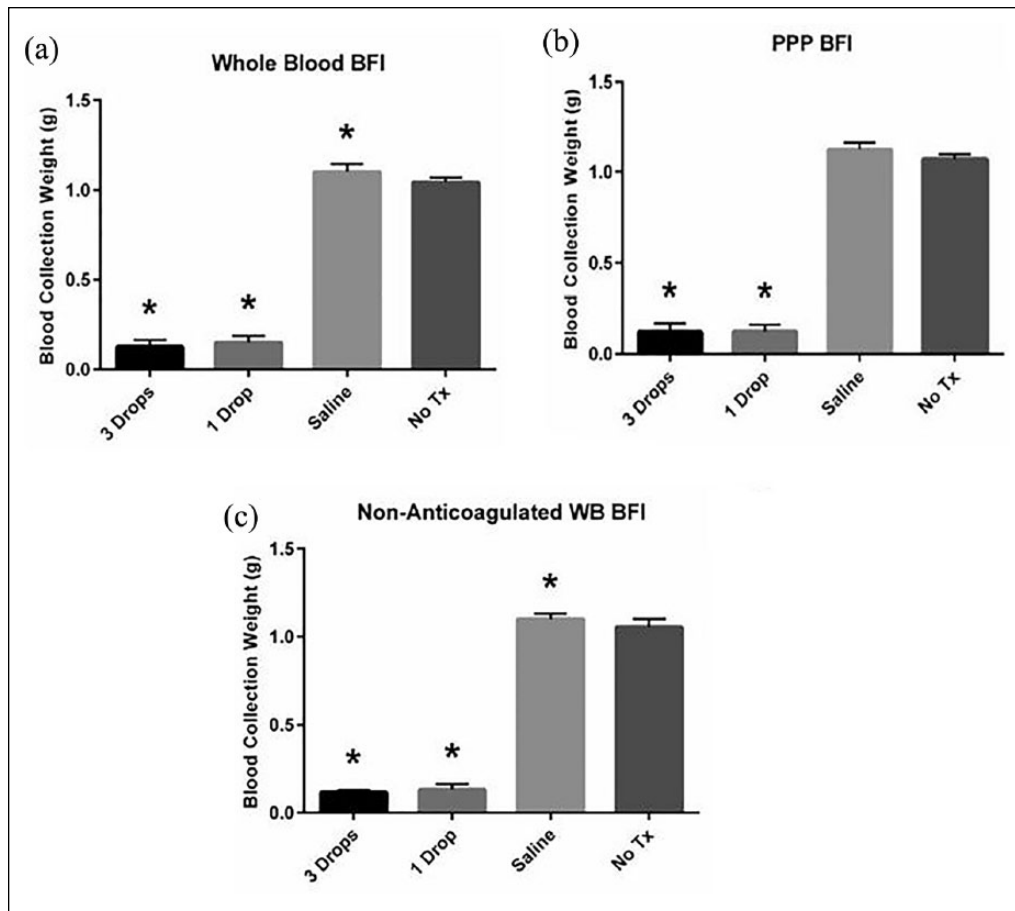


Figure 3. BFI assay on (a) anticoagulated whole blood, (b) PPP, and (c) non-anticoagulated whole blood (3 Drops or 1 Drop—drops of cyanoacrylate, saline, No Tx—no treatment). Asterisk indicates statistically significant differences compared to the No Tx group ($p < 0.05$; $n = 8$).

Table 1. Hemostasis score evaluation.

Score	Evaluation
0 = None	No bleeding is seen from the incision site
1 = Ooze	Blood observed at the edge of the incision site though not flowing
2 = Very slight	Blood trickles very slowly from the incision site
3 = Slight	Blood flows slowly from the incision site
4 = Moderate	Blood flow from the incision site is definite
5 = Severe	Blood flows freely from the incision site steadily

or less effective. All results from this BFI assay are demonstrated in Figure 3.

The intensity of blood flow from the incision, *in vivo*, was recorded based on a scale as shown in Table 1. The same professional scored all sites, and the scores for the test and control articles were directly compared to the SC. The “prior-to-treatment” scores serve as a baseline to determine the effect the different articles have on improving hemostasis at different time points; incision sites throughout the study are

presented in Figure 4. Prior to treatment with cyanoacrylate, the average incision bleeding score was 2.3 ± 1.0 . Cyanoacrylate improved hemostasis at the time points of 3, 6, 9, and 12 min with the average scores of 0.3 ± 0.5 , 0.2 ± 0.5 , 0.2 ± 0.4 , and 0.2 ± 0.4 , respectively. At 3 and 6 min, cyanoacrylate lowered the blood flow by 7 and 11 times the amount, respectively, when compared to the respective “prior-to-treatment” score; this was maintained throughout the remaining time points. Overall, cyanoacrylate successfully acted as a hemostatic agent to reduce blood flow in linear, full-thickness incisions in swine with an overall average post-treatment score of 0.2 ± 1.0 . The average scores at the time points of 3, 6, 9, and 12 min for known HA1 are 0.1 ± 0.5 , 0.2 ± 0.6 , 0.2 ± 0.5 , and 0.2 ± 0.5 , respectively, with an overall post-treatment score of 0.2 ± 0.5 . The average scores at the time points of 3, 6, 9, and 12 min for known HA2 are 0.1 ± 0.6 , 0.2 ± 0.5 , 0.2 ± 0.5 , and 0.0 ± 0.2 , respectively, with an overall post-treatment score of 0.1 ± 0.4 . HA1, HA2, and cyanoacrylate all aided in achieving hemostasis with cyanoacrylate performing statistically equivalent to both known hemostatic products. Cyanoacrylate, HA1, and HA2 all performed statistically

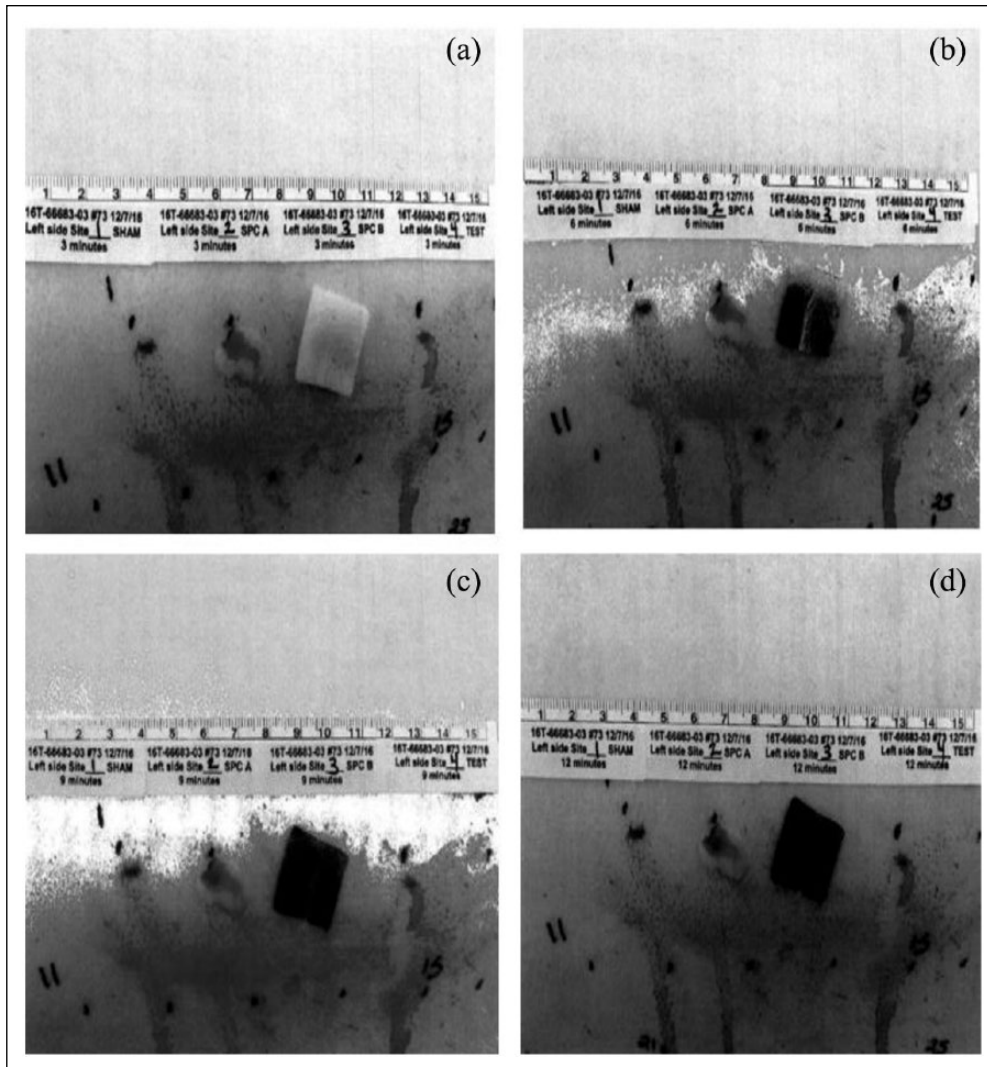


Figure 4. (a) 3 min, (b) 6 min, (c) 9 min, and (d) 12 min after treatment. Each figure contains four incisions, from the left to right: received no treatment, treated with HA1, treated with HA2, and treated with cyanoacrylate.

better than the SC site, having at least three times less bleeding than the SC sites. The results comparing HA1, HA2, cyanoacrylate, and the SC can be seen in Figure 5.

Discussion

During the customized mACT assay, cyanoacrylate, used in the amounts of one and three drops, achieved mechanical hemostasis 12 times quicker than thromboplastin. Cyanoacrylate also achieved mechanical hemostasis significantly faster than the no-treatment group during the customized mACT assay indicating that cyanoacrylate helps decrease the overall amount of time it takes to arrest the continuous flow of blood.

The BFI assay was conducted and the blood collection weight was measured for anticoagulated whole blood, PPP, and non-anticoagulated whole blood. The blood collection contents all decreased to more than seven times

lower upon coming in contact with cyanoacrylate. Cyanoacrylate has the ability to quickly achieve mechanical hemostasis by creating a physical blockade to halt excessive bleeding significantly compared to the no-treatment group, demonstrating one of the most important hemostatic factors.¹³ In addition, a PT assay confirmed that cyanoacrylate does not alter normal coagulation.

In vivo, porcine models historically agree with human studies 78% of the time when representing the human wound healing processes consisting of achieving hemostasis. Therefore, the porcine in vivo model was selected to evaluate cyanoacrylate's hemostatic properties.¹⁷ Cyanoacrylate was compared to HA1, indicated as a hemostatic device and HA2, indicated for the local management of bleeding wounds.^{15,16} Overall, cyanoacrylate, HA1 and HA2 significantly reduced bleeding compared to the SC, demonstrating cyanoacrylate's ability to perform equivalently to current hemostatic products used clinically.

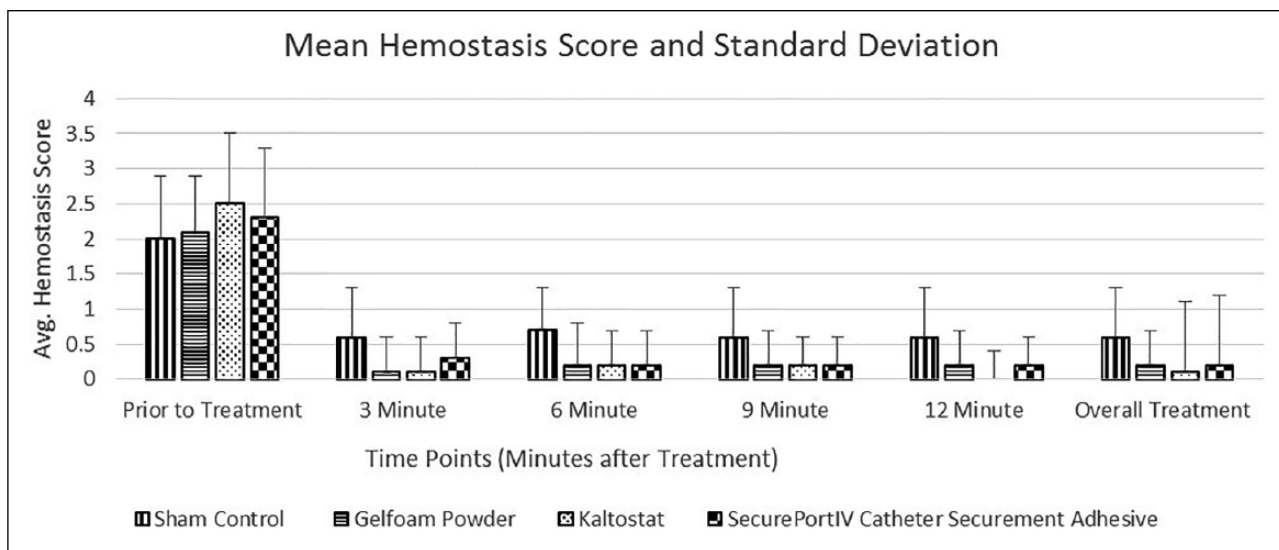


Figure 5. Average hemostasis scores for each treatment per time period.

These novel in vivo and in vitro test methods for determining the hemostatic effect of small amounts of cyanoacrylate confirmed previous literature claims that cyanoacrylate has the ability to be an effective hemostatic agent and further demonstrated that the hemostatic effect of cyanoacrylate is present in small and single-layer amounts, which has not previously been determined.⁶⁻¹³ The cyanoacrylate in the studies reported here has an indication for use to secure intravascular catheters. Complications associated with catheter securement are dislodgment, phlebitis, and CRBSIs and cyanoacrylate has been proven to help reduce these complications by lowering the rate of peripheral intravenous and arterial catheter failure by 10%, with improved fixation on central venous and epidural catheters.^{1,18-20} The hemostatic properties of this cyanoacrylate product will benefit clinicians providing intravenous therapies by aiding in the control of any unwanted bleeding at the catheter insertion site and reducing hematomas.

Our studies are experimental methods and limitations are recognized regarding the sample size and that larger data sets should be tested in the future. During, the in vivo study, even though the cyanoacrylate, HA1, and HA2 products showed significant hemostatic effects compared to the SC, the scores were all <1. The scoring system in future studies should be reflective of this significant difference. It is recommended that further investigations be conducted to focus and demonstrate the hemostatic properties of this novel cyanoacrylate product in a clinical setting.

Conclusion

A use for cyanoacrylate catheter securement adhesive as an effective means of mechanical hemostasis was demonstrated through novel in vitro and in vivo testing methods. Cyanoacrylate achieved consistent inhibition of blood flow

and rapid mACTs attaining mechanical hemostasis in anticoagulated whole blood, PPP, and non-anticoagulated whole blood, demonstrating a significantly faster ACT 12-fold faster than thromboplastin. Statistically, cyanoacrylate performed better than saline in both the assays. In heparinized swine, cyanoacrylate demonstrated hemostatic properties statistically equivalent to those of hemostatic products, HA1 and HA2. Cyanoacrylate also demonstrated hemostatic properties significantly more effective when compared to the untreated SC. Overall, cyanoacrylate demonstrated to be effective in terms of achieving mechanical hemostasis.

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Declaration of conflicting interests

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