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Comparison of Combat Gauze with Fibrin Sealant Patch in Hemorrhage Control after Vascular or Hepatic Trauma



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14. ABSTRACT Noncompressible vascular injury not amenable to the use of a tourniquet remains a significant cause of potentially preventable death on the battlefield. The recent development of fibrin patches, which combine both biologic and nonbiologic hemostatic agents, provides a potential adjunct to the current guidelines for the treatment of these injuries. We examined the effectiveness of a fibrin patch (FP) in comparison to the current standard of Combat Gauze (CG) in an established junctional hemorrhage model. Yorkshire pigs (n=15) were placed under general anesthesia and underwent arterial and venous line placement followed by right femoral vessel exposure. Four pigs were used as controls and underwent line placement and groin incision only. In the remaining 11 pigs, junctional femoral artery hemorrhage was created with a 6-mm aortic punch. After uncontrolled hemorrhage for 45 seconds, wounds were treated with placement of either CG (n=5) or FP (n=6), and 75 pounds of pressure was held for 3 minutes. The pigs were then resuscitated to a mean arterial pressure of 65 using 500 mL of Hextend followed by Ringer's lactate at a rate of 100 mL/min to a maximum of 10 liters. The pigs were followed for 4 hours post-injury during which time they were resuscitated and vital signs were monitored. Mortality, establishment of hemostasis, re-bleeding, blood loss, and fluid resuscitation volumes were recorded for each animal. Comparison of the two groups revealed average blood loss during the hemorrhage of 207 mL for the CG group vs. 225 mL for the FP group (p not significant). Survival in the CG group was 100% and 83% in the FP group (p not significant). Each intervention had a 100% initial hemostasis after release of the 75-pound pressure; however, 66% in the FP group and 40% in the CG group displayed re-bleeding at 3 minutes. Mean total blood loss during the experiment was 316 mL for the CG group and 962 mL for the FP arm (p=0.082). Maintenance of hemostasis after simulated ambulation was 60% in the CG group and 80% in the FP group. Vessel patency was equivalent. Our data suggest that the use of an FP for treatment of vascular injury is equivalent to CG. Additional research and experimentation are needed to determine the role of fibrin patches in acute traumatic hemorrhage control.					
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TABLE OF CONTENTS

Section	Page
LIST OF FIGURES	ii
1.0 SUMMARY.....	1
2.0 BACKGROUND	1
3.0 METHODS	2
3.1 Animal Housing and Preparation	2
3.2 Instrumentation, Injury, Hemodynamic Monitoring, and Laboratory Values	3
3.2.1 Specific Aim 1	3
3.2.2 Specific Aim 2	3
3.3 Statistical Analysis	4
4.0 RESULTS	4
4.1 Specific Aim 1: Compare Performance of CG to EVARREST in a Porcine Model of Vascular Trauma	4
4.2 Specific Aim 2: Compare Performance of CG to EVARREST in a Porcine Model of Hepatic Trauma	4
5.0 DISCUSSION	12
6.0 CONCLUSIONS.....	13
7.0 REFERENCES	13
LIST OF ABBREVIATIONS AND ACRONYMS	14

LIST OF FIGURES

	Page
Figure 1. Equivalent blood loss at hemorrhage, but greater total loss with FP	5
Figure 2. Amounts of fluid administered.....	6
Figure 3. Survival at 4 hours.....	7
Figure 4. Hemostasis at time points during the experiment, including 3 minutes after simulated ambulation	7
Figure 5. Vessel patency at completion of experiment when comparing all that survived	8
Figure 6. Liver injury blood loss comparison between CG and FP.....	9
Figure 7. Percent drop in MAP from baseline before injury to before intervention.....	10
Figure 8. Four-hour survival in both groups was 100%	11
Figure 9. Hemostasis at different time points during the liver injury model.....	11

1.0 SUMMARY

Noncompressible vascular injury not amenable to the use of a tourniquet remains a significant cause of potentially preventable death on the battlefield. The recent development of fibrin patches, which combine both biologic and nonbiologic hemostatic agents, provides a potential adjunct to the current guidelines for the treatment of these injuries. We examined the effectiveness of a fibrin patch (FP) in comparison to the current standard of Combat Gauze (CG) in an established junctional hemorrhage model. Yorkshire pigs (n=15) were placed under general anesthesia and underwent arterial and venous line placement followed by right femoral vessel exposure. Four pigs were used as controls and underwent line placement and groin incision only. In the remaining 11 pigs, junctional femoral artery hemorrhage was created with a 6-mm aortic punch. After uncontrolled hemorrhage for 45 seconds, wounds were treated with placement of either CG (n=5) or FP (n=6), and 75 pounds of pressure was held for 3 minutes. The pigs were then resuscitated to a mean arterial pressure of 65 using 500 mL of Hextend followed by Ringer's lactate at a rate of 100 mL/min to a maximum of 10 liters. The pigs were followed for 4 hours post-injury during which time they were resuscitated and vital signs were monitored. Mortality, establishment of hemostasis, re-bleeding, blood loss, and fluid resuscitation volumes were recorded for each animal. Comparison of the two groups revealed average blood loss during the hemorrhage of 207 mL for the CG group vs. 225 mL for the FP group (p not significant). Survival in the CG group was 100% and 83% in the FP group (p not significant). Each intervention had a 100% initial hemostasis after release of the 75-pound pressure; however, 66% in the FP group and 40% in the CG group displayed re-bleeding at 3 minutes. Mean total blood loss during the experiment was 316 mL for the CG group and 962 mL for the FP arm (p=0.082). Maintenance of hemostasis after simulated ambulation was 60% in the CG group and 80% in the FP group. Vessel patency was equivalent. Our data suggest that the use of an FP for treatment of vascular injury is equivalent to CG. Additional research and experimentation are needed to determine the role of fibrin patches in acute traumatic hemorrhage control.

2.0 BACKGROUND

Hemorrhage remains the most common cause of potentially survivable mortality on the battlefield [1]. Current Tactical Combat Casualty Care Committee guidelines include the use of QuickClot Combat Gauze™ (ZMedica, Wallingford, CT) dressing for compressible extremity hemorrhage. Combat Gauze (CG) functions well in this setting and provides an important adjunct to hemostasis. In addition, CG is commonly used in an “off label” fashion, in both the military and civilian settings, for adjunct control of internal hemorrhage, such as large liver lacerations, but this use is limited by the handling properties of the product as well as the requirement for removal.

The Food and Drug Administration recently approved EVARREST™ (Johnson & Johnson, New Brunswick, NJ) for “use with manual compression...during open...surgery” [2]. EVARREST is a biologic fibrin sealant patch that consists of plasma-derived human fibrinogen and thrombin backed by layers of oxidized cellulose and polyglactin 910 to allow conformation to raw surfaces. Early anecdotal experiences with this product suggest that this may be a significant step forward in the realm of hemostatic adjuncts. One additional potential advantage of this product is that, when used internally, it can be allowed to remain in place permanently and does not require extirpation at subsequent operation. Despite Food and Drug Administration

approval for a broad range of “bleeding” situations, this product has not been rigorously tested in the setting of significant traumatic hemorrhage, such as that encountered during the initial phases of combat casualty care and transport.

Previous studies have validated the effectiveness of CG in decreasing hemorrhage from vascular injuries [3]. Additional work has suggested that the use of fibrin patches (FP) can decrease hemorrhage and mortality in traumatic injury [4], but the two have not been compared directly. This project directly compared the performance of EVARREST with CG in two porcine models of trauma and hemorrhage. **Our overall hypothesis was that EVARREST would be superior to CG for use for internal hemorrhage.** To test this hypothesis, we proposed two specific aims:

1. **Specific Aim 1:** Compare performance of CG to EVARREST in a porcine model of vascular trauma. These experiments utilized a porcine model of vascular trauma followed by resuscitation with Hextend and crystalloid to test the hypothesis that EVARREST is superior to CG following arterial hemorrhage.
2. **Specific Aim 2:** Compare performance of CG to EVARREST in a porcine model of hepatic trauma. These experiments utilized a porcine model of hepatic trauma and hemorrhage trauma followed by resuscitation with Hextend and crystalloid to test the hypothesis that EVARREST is superior to CG following trauma and hemorrhage.

By answering these questions, we hope to provide guidelines for potential use of EVARREST during severe hemorrhage.

3.0 METHODS

3.1 Animal Housing and Preparation

All animal protocols were in accordance with the National Institutes of Health guidelines and were approved by the University of Cincinnati Institutional Animal Care and Use Committee. Fifteen female Yorkshire pigs were obtained from a local vendor (Isler Genetics, Prospect, OH) and allowed to acclimate in our facility for at least 48 hours. Animals were housed 1-2 per cage on standard bedding with food and water ad libitum. Food was withheld overnight the night before the procedure but water was not. All experiments were performed in the University of Cincinnati Center for Surgical Innovation surgical suite, Cincinnati, OH, beginning between 7 and 9 a.m. On the day of the procedure, animals were sedated with intramuscular 5 mg/kg telazol and 1 mg/kg xylazine (Henry Schein Animal Health, Dublin, OH), orotracheally intubated, positioned supine, and mechanically ventilated with a standard anesthesia ventilator (Ohmeda 7000, Ohmeda, Inc., Madison, WI) using standardized ventilator settings (inspired fraction of oxygen (F_iO_2) 1.0, tidal volume 10 mL/kg, positive end-expiratory pressure 5 cm H_2O , respiratory rate adjusted to achieve a target end-tidal carbon dioxide tension of 35 ± 5 mmHg). We kept the F_iO_2 constant at 1.0 for all animals throughout the study to maintain consistency between animals and to avoid hypoxia during intermittent periods where pulse oximetry readings were lost secondary to hypotension. Anesthesia was maintained with inhaled isoflurane (Henry Schein Animal Health, Dublin, OH) for the duration of the study.

3.2 Instrumentation, Injury, Hemodynamic Monitoring, and Laboratory Values

All animals underwent cannulation of the following vessels: right external jugular vein with 16-gauge angiocath and right internal carotid artery with a 20-gauge catheter (Teleflex Inc., Research Triangle Park, NC). This allowed for continuous blood pressure monitoring and laboratory draws via the arterial line and a route for administration of resuscitative fluids via the venous line. Injury was then created as follows based on specific aim being addressed.

3.2.1 Specific Aim 1. Compare performance of CG to EVARREST in a porcine model of vascular trauma. Animals were separated into three groups:

1. *Control:* Arterial and venous cannulation and right femoral cutdown without injury
2. *CG intervention:* Arterial and venous cannulation with right femoral cutdown with injury, free bleed; intervention with CG and one laparotomy sponge
3. *FP intervention:* Arterial and venous cannulation with right femoral artery cutdown with injury and free bleed; intervention with FP and two laparotomy sponges

A right femoral cutdown was performed to expose the right femoral artery. Once isolated, it was submerged in 5 mL of 1% lidocaine for 60 seconds to minimize vasospasm. Vascular clamps were then placed to isolate a 3-cm section of artery where a 6-mm aortic punch was used to create the injury. Uncontrolled hemorrhage was allowed for 45 seconds. One minute was then allowed for intervention with CG or FP and laparotomy sponge followed by 3 minutes of compression by application of 75-pound dumbbell weight over the wound site. After compression, the adjunct product and sponge were left in place for the remainder of the experimental period. During this time, the animals were resuscitated initially with 500 mL of Hextend followed by Ringer's lactate at a rate of 100 mL/min to a maximum of 10 liters to maintain a mean arterial pressure (MAP) of greater than 60 mmHg.

3.2.2 Specific Aim 2. Compare performance of CG to EVARREST in a porcine model of hepatic trauma. Animals were separated into three groups:

1. *Control:* Arterial and venous cannulation followed by laparotomy with liver injury and laparotomy sponge packing
2. *CG intervention:* Arterial and venous cannulation followed by laparotomy with liver injury treated with CG anteriorly and posteriorly with laparotomy sponge packing
3. *FP intervention:* Arterial and venous cannulation followed by laparotomy with liver injury treated with FB anteriorly and posteriorly with laparotomy sponge packing

A standard length (20-cm) midline incision was created starting at the xyphoid process and extending inferiorly. Grade 5 liver injury was created using the model originally described and standardized by Holcomb et al. [5]. After bleeding freely for 2 minutes, animals were randomized into one of the three groups above. Pressure was applied for a period of 3 minutes, followed by closure of the abdomen. Animals were resuscitated initially with 500 mL of Hextend followed by Ringer's lactate at a rate of 100 mL/min to a maximum of 10 liters to maintain a MAP of greater than 60 mmHg.

At the end of the resuscitation phase, abdomens were reopened to evaluate for additional blood loss and evaluation of injury after removal of intervention. Animals were then euthanized. All animals received a continuous infusion of Ringer's lactate solution at 25 mL/h for the duration of the study to maintain catheter patency. Initial mortality, blood loss, and re-bleeding rates were measured during a subsequent 4-hour observation period. Standard vital signs – heart rate, rectal temperature, MAP, and peripheral oxygen saturation by pulse oximetry – were recorded every 15 minutes. Arterial blood gases, arterial lactate, and acid-base status – pH, base excess, serum bicarbonate, and arterial oxygen saturation – were measured with a VetScan i-STAT point-of-care analyzer (Abaxis, Union City, CA) at baseline and then every hour during the resuscitation phase. Hemoglobin and international normalized ratio were measured with i-STAT at baseline and hourly during resuscitation phase. Thromboelastography was measured at baseline and immediately prior to euthanasia.

3.3 Statistical Analysis

SigmaPlot version 11.0 was utilized for statistical comparisons (Systat Software, San Jose, CA). All data are presented as mean \pm standard deviation. Statistical comparisons between groups were made by Kruskal-Wallis test with Dunn's test for post hoc pairwise comparisons where appropriate. Significance was defined prior to analysis as $p < 0.05$. The data were analyzed in a single batch after the completion of all experimental groups.

4.0 RESULTS

4.1 Specific Aim 1: Compare Performance of CG to EVARREST in a Porcine Model of Vascular Trauma

Comparison of the two intervention groups revealed average blood loss during the hemorrhage of 207 mL for the CG group vs. 225 mL for the FP group ($p = \text{NS}$) (Figure 1). Differences in the amounts of fluid administered between the CG and FP groups were not statistically significant (Figure 2). Survival in the CG group was 100% and 83% in the FP group ($p = \text{NS}$) (Figure 3). Each intervention had a 100% initial hemostasis after release of the 75-pound pressure; however, 66% in the FP group and 40% in the CG group displayed re-bleeding at 3 minutes (Figure 4). Mean total blood loss during the experiment was 316 mL for the CG group and 962 mL for the FP arm ($p = 0.082$) (Figure 1). Maintenance of hemostasis after simulated ambulation was 60% in the CG group and 80% in the FP group (Figure 4). Vessel patency was equivalent (Figure 5).

4.2 Specific Aim 2: Compare Performance of CG to EVARREST in a Porcine Model of Hepatic Trauma

Comparison of the two groups revealed average blood loss during the hemorrhage of 408 mL for the CG group vs. 507 mL for the FP group ($p = \text{NS}$) (Figure 6). Average drop in MAP was 24% for the CG group and 28% for the FP group ($p = \text{NS}$) (Figure 7). Survival in each group was 100% (Figure 8). Each intervention demonstrated 100% initial hemostasis after release of the 3 minutes of manual pressure. All subjects in the CG and FP groups demonstrated hemostasis at the 4-hour time point. All re-bled with removal of the product (Figure 9).

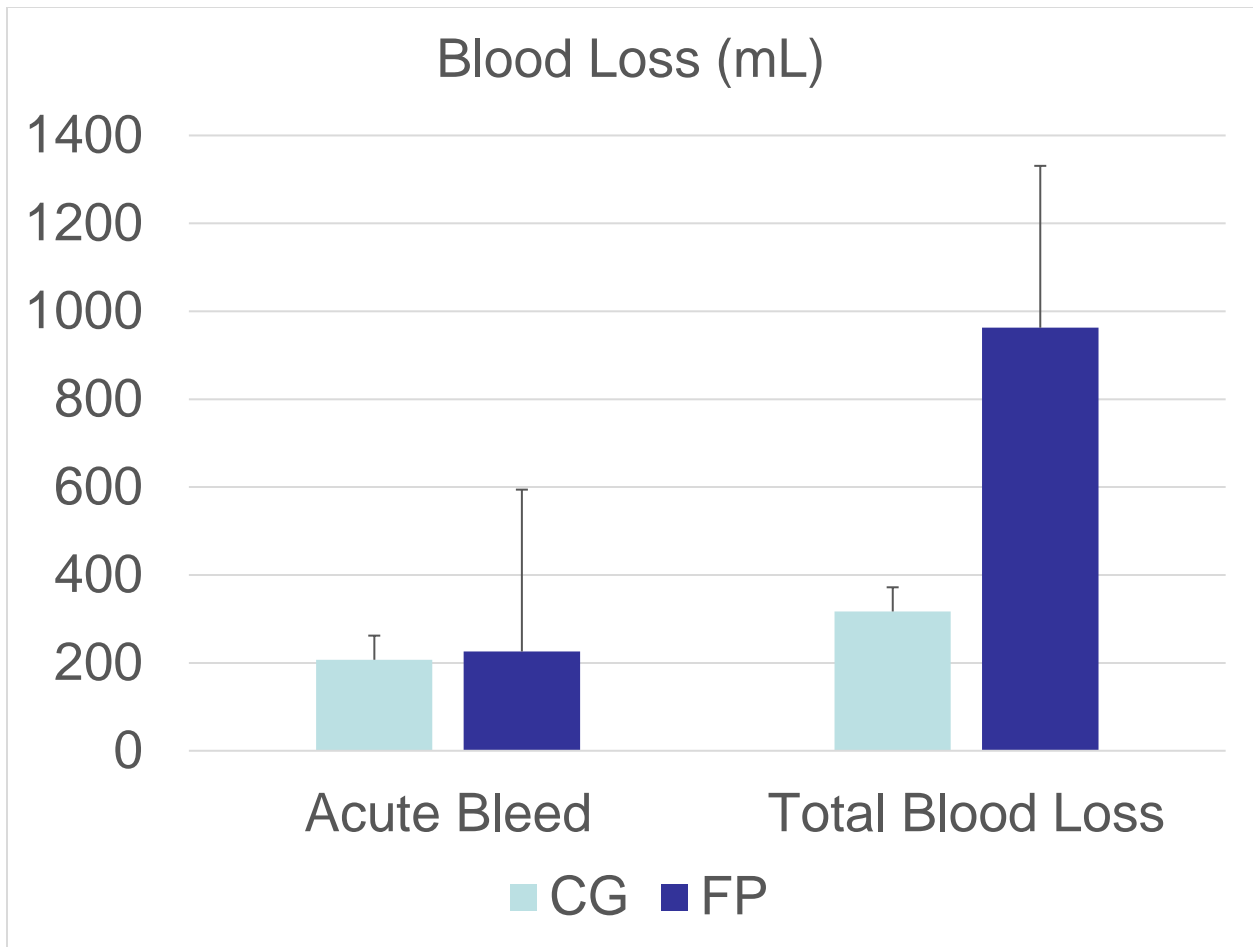


Figure 1. Equivalent blood loss at hemorrhage, but greater total loss with FP.
Differences were not statistically significant.

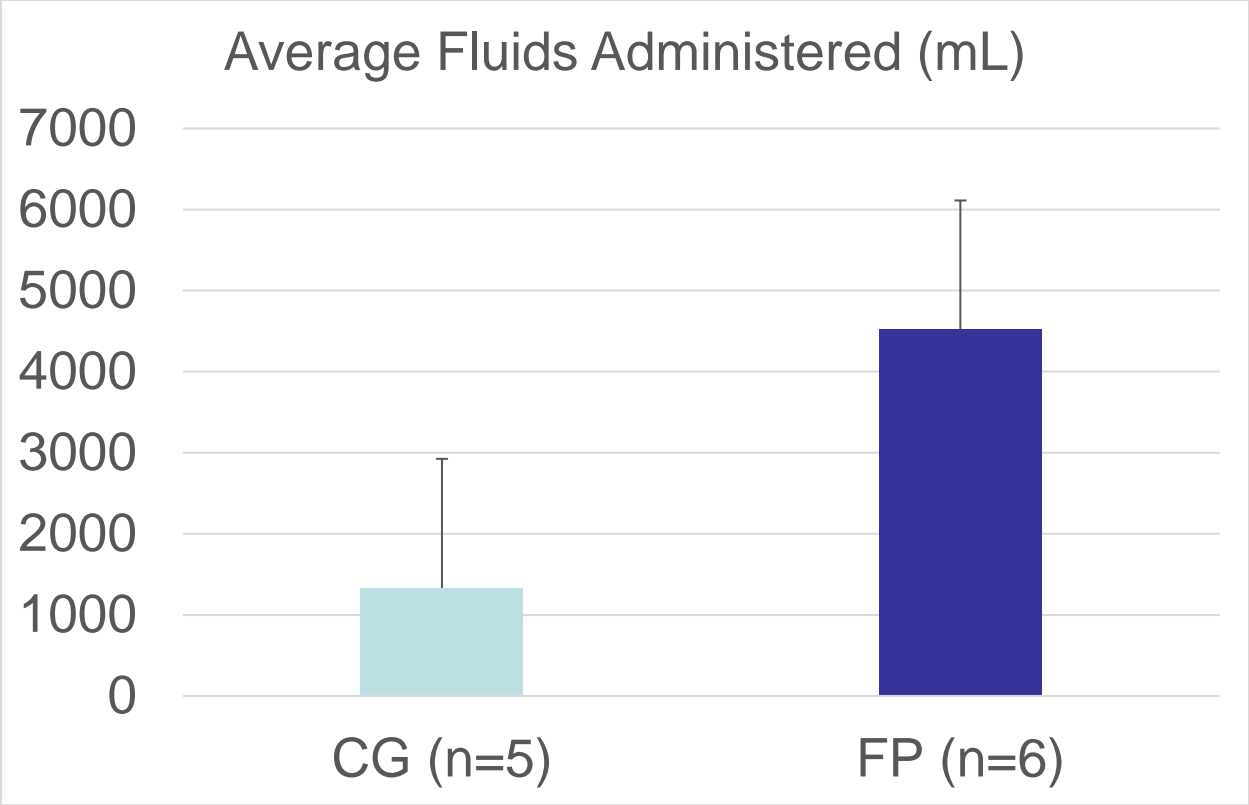


Figure 2. Amounts of fluid administered. *Differences were not statistically significant.*

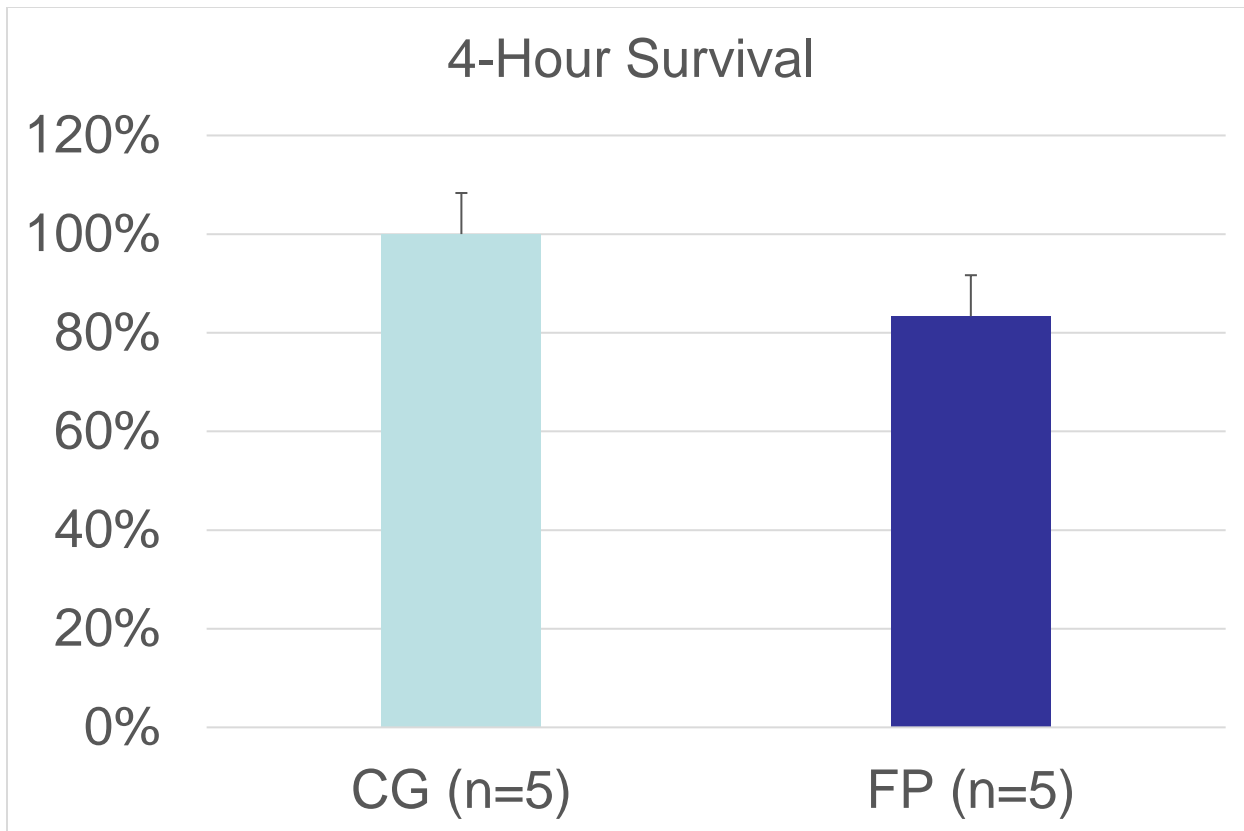


Figure 3. Survival at 4 hours. *Differences were not statistically significant.*

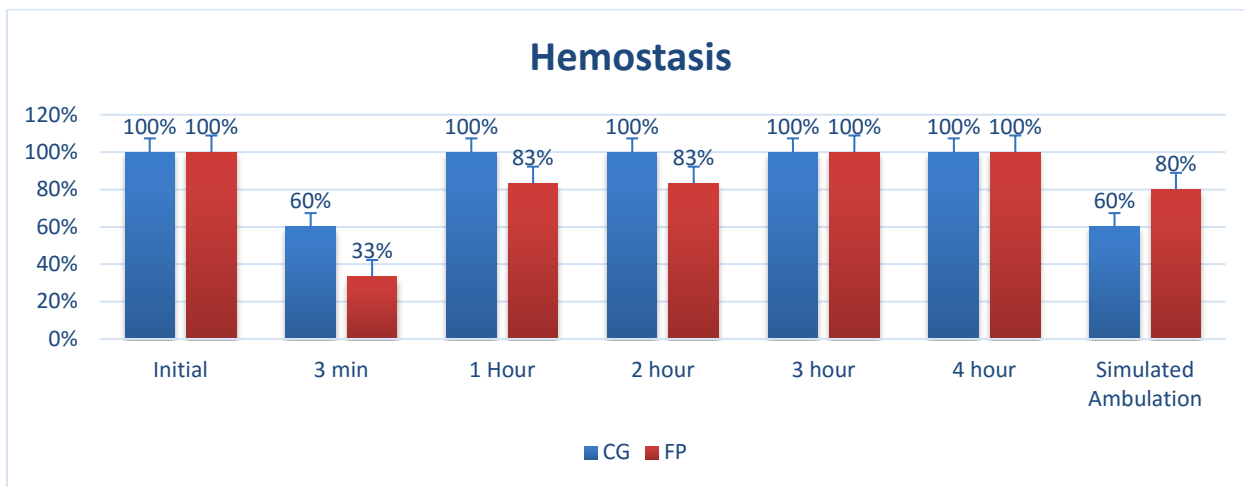


Figure 4. Hemostasis at time points during the experiment, including 3 minutes after simulated ambulation. *Differences were not statistically significant.*

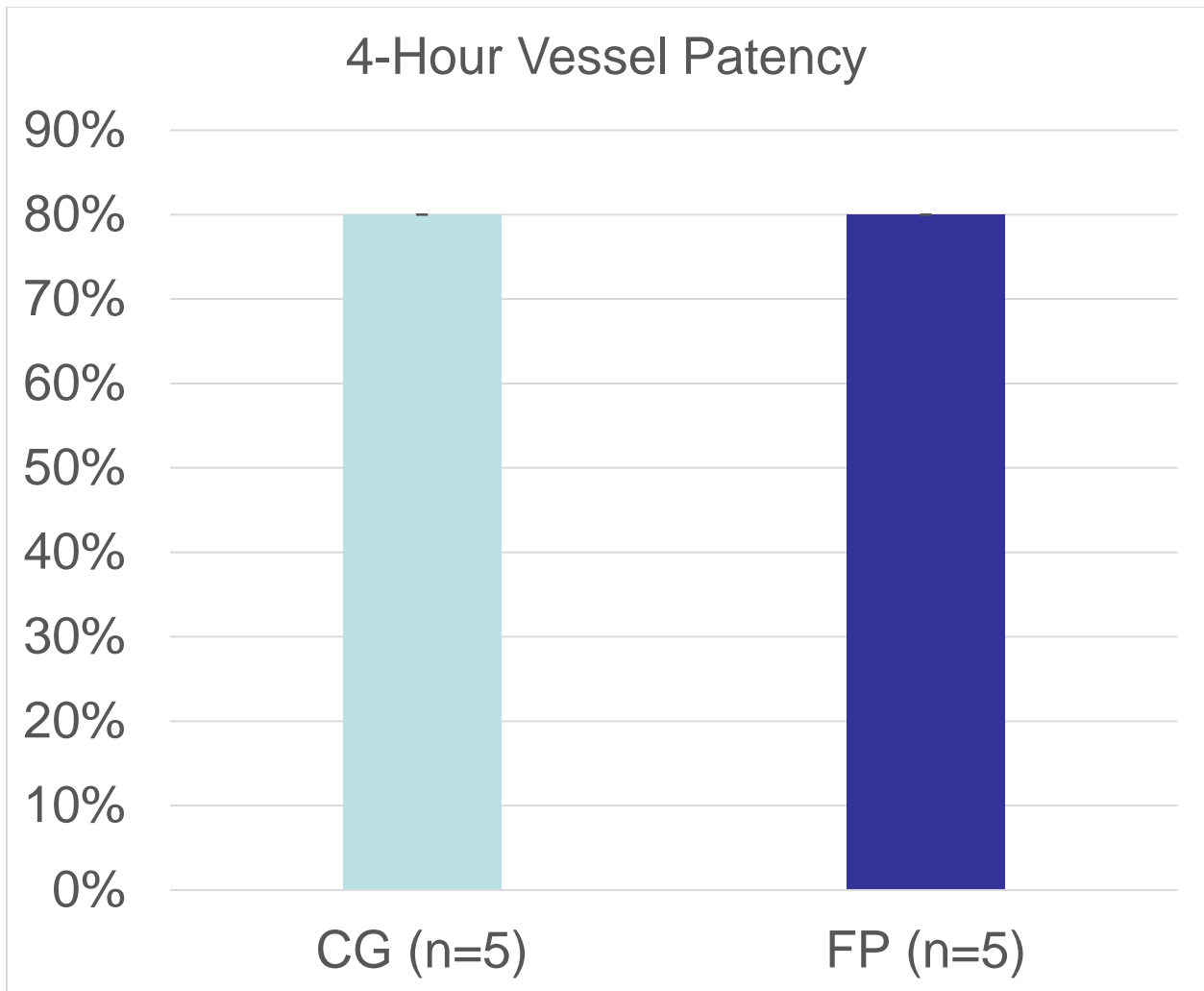


Figure 5. Vessel patency at completion of experiment when comparing all that survived.
Differences were not statistically significant.

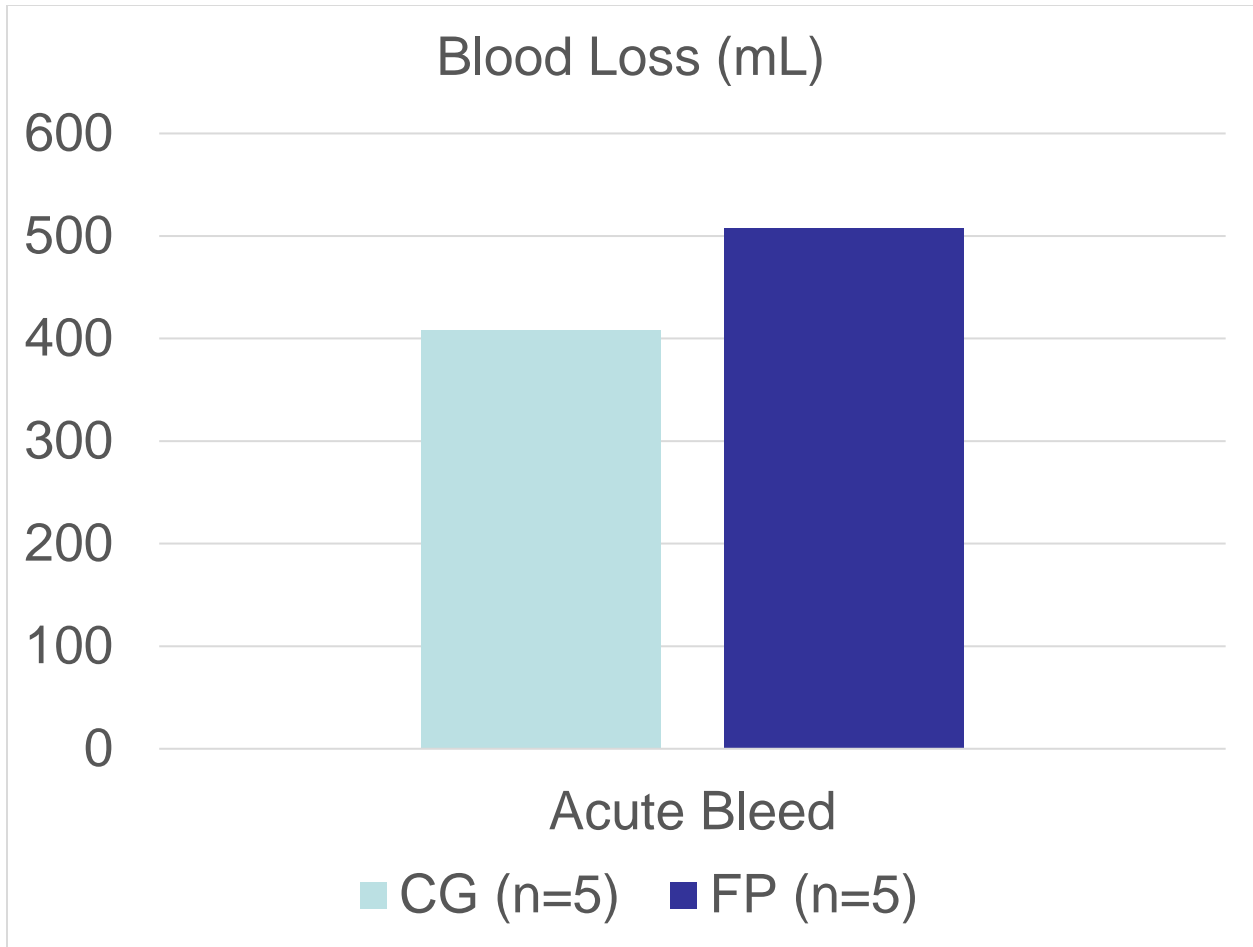


Figure 6. Liver injury blood loss comparison between CG and FP. Total blood loss during experiment. Differences were not statistically significant.

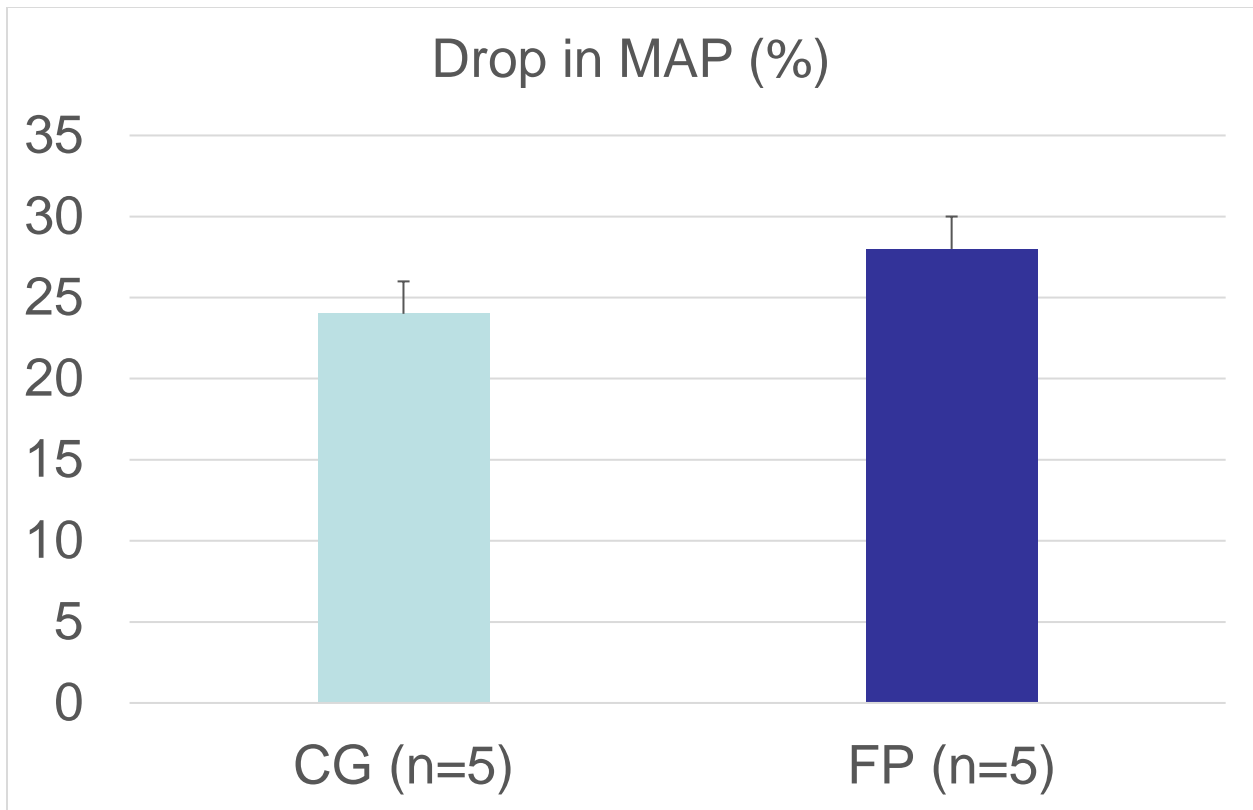


Figure 7. Percent drop in MAP from baseline before injury to before intervention.
Differences were not statistically significant.

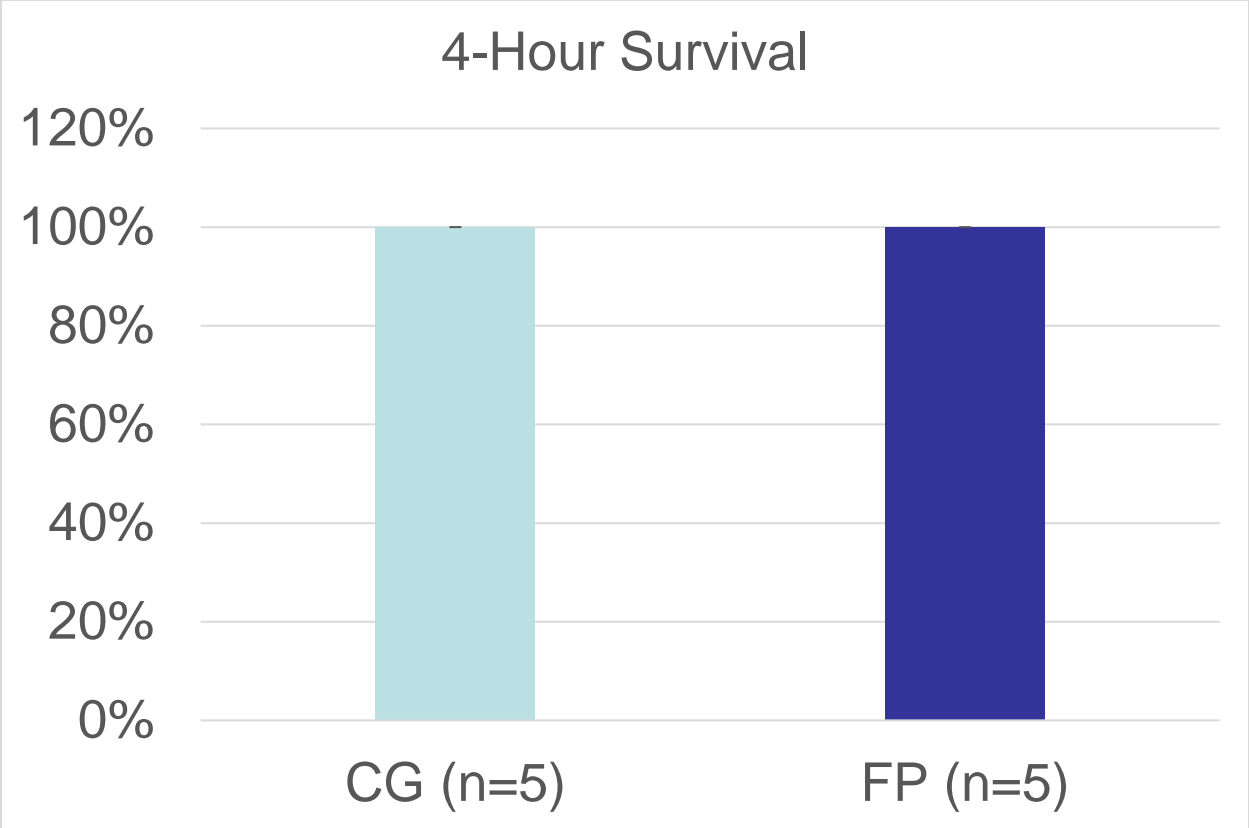


Figure 8. Four-hour survival in both groups was 100%.

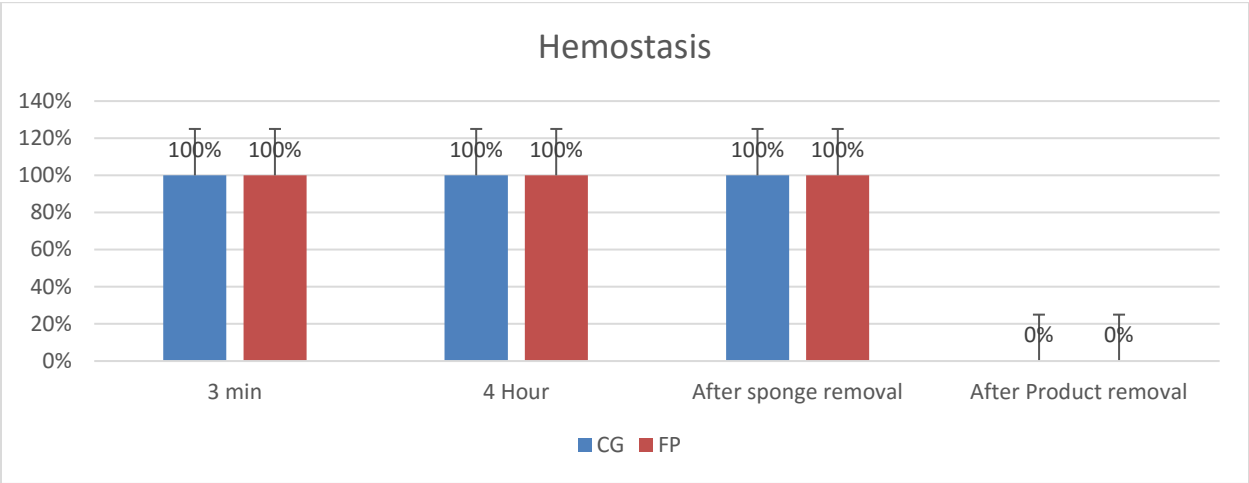


Figure 9. Hemostasis at different time points during the liver injury model. No differences were observed.

5.0 DISCUSSION

In the present series of experiments, we compared the efficacy of CG and an FP in controlling hemorrhage in established porcine models of junctional vascular injury and grade 5 liver injuries. We found that the FP would perform comparably to the established standard of CG.

The rationale for our study design was as follows. CG has been used in both liver injury and junctional hemorrhage and has shown success. The recent development of combination hemostats that incorporate both biologic and nonbiologic agents gives pause as to how these agents can be used in the care of the combat casualty. Our initial approach was to see if the FP could accomplish the level of hemostasis demonstrated by CG in established models. If this could be established, then evaluation of which product should be used in which situation based on distinct product characteristics, locations of bleed, difficulty in application, and cost should be considered next.

Our study has answered the first question. In the junctional hemorrhage model, we were able to demonstrate that there was no statistical difference in mortality, blood loss, fluid administration, or re-bleeding throughout the experimental time period. In practice, a junctional hemorrhage from a penetrating injury to the groin is much different than a femoral artery cutdown with 6-mm punch injury. We suspect that while application in the controlled experimental model of the FP showed equivalent results to CG, the ability to have apposition of the patch to the edges of the bleeding structure in a real injury would be compromised, resulting in a higher failure rate.

In terms of the liver injury, the application of both CG and the FP showed excellent ability to establish and maintain hemostasis. Results in terms of hemostasis and mortality were equal. Differences between the two groups in blood loss and drop in MAP, while present, were not statistically significant. The internal use of CG is an off-label, but commonly performed, maneuver. While application of the FP in a real junctional hemorrhage situation may be difficult, that is not the case in a liver injury. The interesting finding here was that at the 4-hour mark, both products demonstrated hemostasis while in place. Once removed, all livers began bleeding again. One of the novel characteristics of the FP is that it can be left in place, whereas the CG and laparotomy sponges must be removed. This may be a niche where the FP has a significant advantage over CG.

There are several limitations of the present study, and our data should be interpreted with caution. The junctional hemorrhage model used is the accepted U.S. Army Institute of Surgical Research (USAISR) model. With the strict application requirements of the FP, visualization of the vascular injury is necessary. While this is possible in the USAISR model, it may not be realistic in a combat situation with penetrating junctional trauma. Our finding of equivalence in the animal model may not translate to equivalence in theatre; thus, we suspect that CG would prove to be superior in this setting. When examining the liver injury, our model was based on the standardized USAISR grade 5 liver injury. We were able to meet the percent drop in MAP in all subjects, but had no mortality in any group over the 4-hour experimental time period. This may speak to the efficacy of both CG and the FP, but it may also be due to a lower grade injury than expected.

6.0 CONCLUSIONS

The use of an FP when compared to CG in established junctional hemorrhage and grade 5 liver injury models has equivalent outcomes when looking at blood loss, mortality, and resuscitation requirements. Each product has specific advantages and disadvantages. CG has the ability to be packed into holes and deep spaces but requires removal, whereas the FP needs to be carefully applied, but can be left in place. While our suspicion is that the FP would not work in a true junctional hemorrhage resulting from a gunshot wound to the groin, creation of a more realistic model would be beneficial in analyzing this objectively.

Equivalent survival and hemostasis in the liver injury model may demonstrate a potential benefit of the FP. If initially placed and hemostasis is obtained, can it be left in place with closure of the abdomen and survival of the animal without need for re-exploration and removal as is needed with CG? If so, this eliminates complications and costs associated with open abdomens and repeat laparotomy. This could be objectively examined in a porcine model similar to what we have already done with some modifications.

7.0 REFERENCES

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LIST OF ABBREVIATIONS AND ACRONYMS

CG	Combat Gauze
F_iO₂	inspired fraction of oxygen
FP	fibrin patch
MAP	mean arterial pressure
USAISR	U.S. Army Institute of Surgical Research