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Percutaneous delivery of self-propelling hemostatic powder for managing non-compressible abdominal hemorrhage: a proof-of-concept study in swine

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ABSTRACT

Introduction: Non-compressible intra-abdominal hemorrhage (NCIAH) is a major cause of preventable death on the battlefield and in civilian trauma. Currently, it can only be definitively managed with surgery, as there are limited strategies for controlling ongoing NCIAH in the prehospital environment. We hypothesized that a self-propelling thrombin-containing powder (SPTP) could increase survival in a swine model of NCIAH when delivered percutaneously into the closed abdomen using an engineered spray system.

Materials and Methods: Nineteen swine underwent surgical laparotomy followed by a Grade V liver injury that created massive hemorrhage, before closing the abdomen with sutures. Animals either received treatment with standard of care fluid resuscitation (n=9) or the SPTP spray system (n=10), which consisted of a spray device and a 14 Fr catheter. Using the spray system, SPTP was delivered into a hemoperitoneum identified using a focused assessment with sonography in trauma (FAST) exam. Lactated Ringer's solution was administered to all animals to maintain a mean arterial pressure (MAP) of >50 mmHg. The primary outcome was percentage of animals surviving at three hours following injury.

Results: In the swine model of NCIAH, a greater percentage of animals receiving SPTP survived to three hours, although differences were not significant. The SPTP spray system increased the median survival of animals from 1.6 hr in the fluid resuscitation group to 4.3 hr. The SPTP spray system delivered a total mass of 18.5 ± 1.0 g of SPTP. The mean change in intra-abdominal pressure following SPTP delivery was 5.2 ± 1.8 mmHg (mean ± SEM). The intervention time was 6.7 ± 1.7 min. No adverse effects related to the SPTP formulation or the spray system were observed. SPTP was especially beneficial in animals that had either severely elevated lactate concentrations or low mean arterial pressure of <35 mmHg shortly after injury.

Conclusions: This demonstrates proof-of-concept for use of a new minimally invasive procedure for managing NCIAH, which could extend survival time to enable patients to reach definitive surgical care.

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Introduction

Uncontrolled hemorrhage following trauma causes half a million deaths globally each year [1]. Hemorrhage is also a leading cause of death on the battlefield, accounting for 91% of potentially preventable deaths [2]. In civilians and on the battlefield, more than one third of all deaths due to hemorrhage are from non-compressible intra-abdominal hemorrhage (NCIAH) [2–5]. NCIAH can currently only be definitively managed with surgery, [2,6] and there are limited strategies in the prehospital environment that can extend survival to enable patients to reach surgery [3,7]. Strategies such as resuscitative endovascular balloon occlusion of the aorta (REBOA) are limited by the advanced technical skills needed to use them and are associated with life-threatening complications [8]. Failure to rapidly control hemorrhage can promote trauma-induced coagulopathy, which occurs in up to 35% of trauma patients and leads to four-fold higher mortality [9,10].

Topical hemostatic agents, such as fibrin sealants and other thrombin-containing agents, could trigger clotting within the abdominal cavity to halt bleeding, and are regularly used in surgery [11,12]. However, managing NCIAH with these agents is difficult because large volumes of pooled and flowing blood act as a barrier which prevent hemostatics from achieving sufficient contact with injured tissues [13,14]. Interventions are needed that can be performed using minimally invasive techniques, and can transport potent hemostatic agents through pooled and flowing blood. This would complement existing technologies for controlling NCIAH [15,16].

We have previously developed a dry, self-propelling thrombin-containing powder (SPTP), also known as CounterFlow, that consists of microparticles of calcium carbonate ($CaCO_3$) formulated with thrombin and tranexamic acid (TXA). SPTP generates CO_2 gas when it contacts aqueous media such as blood. CO_2 generation disperses thrombin and TXA throughout pooling and against flowing blood to achieve hemostasis. It has stopped bleeding in multiple swine and sheep models of hemorrhage, including a lethal model of junctional hemorrhage without compression, and hemorrhage from the carotid artery [17–21].

Here, we aimed to test if SPTP could manage NCIAH because of its ability to spread throughout pooled blood, transport and deliver hemostatics, and produce CO_2 that could increase pressure on the wound. We engineered a minimally invasive delivery system that uses a spray device, and a catheter placed percutaneously using the ultrasound-guided Seldinger technique, to administer SPTP into the abdomen (Fig. 1). We hypothesized that delivering SPTP with this device would increase survival in a swine model of NCIAH compared to a standard of care fluid resuscitation group.

Materials and methods

SPTP preparation

SPTP loaded with recombinant thrombin (Baxter, Deerfield, IL) was prepared using established laboratory scale techniques, as previously described [21]. Briefly, $CaCO_3$ microparticles (3 µm, American Elements, Los Angeles, CA), thrombin, and other excipients were suspended at 100% w/v in saline (10 g/L NaCl, 3 g/L glycine, pH 7.4). The particles were frozen and lyophilized at -105°C and < 200 mTorr. Tranexamic acid (Chem-Impex International, Wood Dale, IL) was protonated and dissolved in distilled water containing excipients and lyophilized. The acidity of the final dry mixture was adjusted by incorporating a physiologically acceptable tricarboxylic acid. Powders underwent particle size reduction and were mixed. SPTP had a final thrombin concentration of 1000 IU/g.

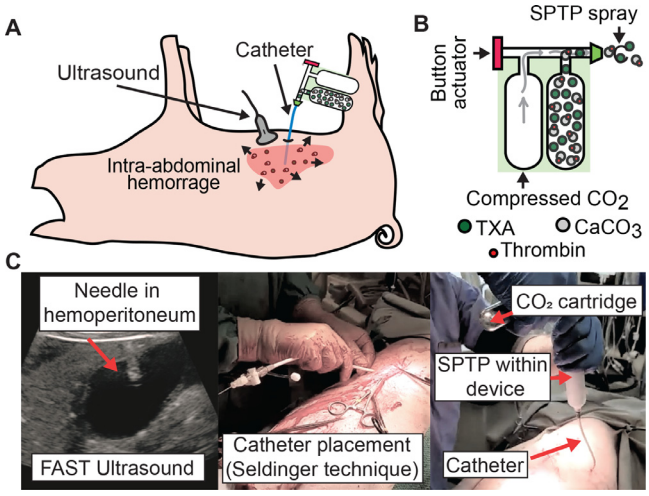

Fig. 1. Using SPTP and a minimally invasive intervention for managing NCIAH. (A) Schematic of SPTP for NCIAH, with the catheter placed percutaneously into the closed abdomen using the Seldinger technique, while guided by FAST ultrasound. (B) Schematic of the catheter-spray applicator which uses compressed CO_2 to pass SPTP through a narrow catheter (C) Photos of SPTP being administered into a pig with NCIAH; from left to right: guidewire access needle inserted into hemoperitoneum under ultrasound visualization, 14 Fr catheter inserted into the hemoperitoneum, SPTP delivery.

SPTP spray system design and construction

The spray system consisted of a handheld spray device, based on turbulent flow aerosolization, which propelled powder through a 14 Fr pigtail catheter (Cat. # G56535, Cook Medical, Bloomington, IN) using compressed CO_2. SOLIDWORKS 2020 (SolidWorks Corp, Waltham, MA) was used for rapid prototyping of the spray device and novel designs were 3D printed by stereolithography and evaluated *in vitro*. SPTP was delivered via short bursts of CO_2 from a portable 12 g cartridge with a user-controlled flow actuator.

Preparing animals for the NCIAH closed-abdomen bleeding model

This experiment was approved by the St. Michael's Hospital Animal Care Committee (Protocol #104) and performed according to the guidelines of the Canadian Council on Animal Care. Female Yorkshire swine weighing 25-35 kg arrived at the animal facility 3-5 days before the procedure. The pigs were fasted overnight before the procedure. Animals were anesthetized by inhalation of 5% isoflurane followed by intubation and mechanical ventilation. Anesthesia was maintained by 2-3% isoflurane. Animals were monitored via jaw tone, pulse oximetry and electrocardiogram (ECG). Core body temperature was measured by a thermometer placed in the esophagus. The left carotid artery was catheterized for intra-arterial blood pressure monitoring and blood sampling. The left jugular vein was catheterized for central venous pressure monitoring and used for Lactated Ringer's infusion. A bladder catheter equipped with a pressure sensor was placed for measuring intra-abdominal pressure (IAP). Baseline vitals and blood samples were taken prior to further procedures.

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Injury creation and animal care for the NCIAH closed-abdomen bleeding model

This model was adapted from a previously published swine model of liver hemorrhage [22]. To produce dilutional coagulopathy, a controlled hemorrhage was performed until animals reached a hypotensive mean arterial pressure (MAP) of <50 mmHg. Then, 1 L of Lactate Ringers solution was infused over ten minutes. A laparotomy was performed, followed by a splenectomy to prevent autotransfusion. Bleeding from the laparotomy or splenectomy-associated complications was aspirated from the abdominal cavity. The left medial lobe of the liver was exposed and scissors were used to fully excise a 10 cm x 3 cm rectangular segment on the distal edge to create a Grade V liver injury causing severe hemorrhage. The laparotomy was rapidly closed using sutures within 2 minutes, and 1 gram of TXA (33 mg/kg) [23] was infused intravenously, which has been used in other swine models of severe hemorrhage [24] and is a similar dose to current Tactical Combat Casualty Care (TCCC) guidelines [25]. Animals were split into two groups: a standard of care fluid resuscitation group and a SPTP group. In both groups, fluid resuscitation with Lactated Ringer's was given to maintain a MAP of >50 mmHg, with up to a maximum of 10 L administered. The primary outcome was the percentage of animals in each group surviving at three hours post-liver injury. Animals surviving at three hours were monitored up to six hours as a secondary outcome. Other secondary outcomes were the heart rate, MAP, end tidal CO_2 ($EtCO_2$), blood coagulation panel parameters, serum lactate concentrations, and fluid volumes administered over survival time.

SPTP delivery

Animals in the SPTP group received up to 20 g of SPTP using the minimally invasive spray system. After closing the laparotomy, animals underwent the focused assessment with sonography in trauma (FAST) exam [26,27], which identified free fluid representing hemoperitoneum surrounding the liver. The closed-abdomen Seldinger technique was used to position a 14 Fr catheter within the hemoperitoneum, after which the spray device loaded with SPTP was attached to the catheter and SPTP was administered into the hemoperitoneum. The mass of SPTP delivered was quantified by subtracting the final mass of the SPTP loaded spray device from the initial mass. The time to deliver SPTP was defined as the time elapsed between the first spray and the last spray of SPTP, after which the spray device was disconnected from the catheter. The change in IAP recorded was the difference between IAP pre-liver injury and the IAP at death.

Histopathology

After euthanasia organs were grossly inspected. Sections of liver proximal to the injury site, lung and kidney were fixed in 10% formalin. Sections were stained with hematoxylin/eosin and Martius Scarlet Blue. Slides were reviewed by two anatomic pathologists blinded to which animals received SPTP and to experimental outcome. The quantity and maturity of blood clot overlying the liver sections was qualitatively evaluated. Hepatic, lung, and renal tissues were evaluated for inflammation, ischemia, necrosis, and intravascular thrombosis.

Scanning electron microscopy

Blood clots were harvested from the intraperitoneal space of animals that received only fluid resuscitation or SPTP, and were prepared as previously described [28]. Briefly, clots were fixed in sodium cacodylate buffer containing 2% glutaraldehyde. They were dehydrated with graded ethanol starting from 30% through absolute ethanol, dried with hexamethyldilazane, and then sputter coated with Au/Pd alloy (Polaron e5100 sputter coater). High resolution images were obtained from random areas of the sample using a Quanta FEG 250 scanning electron microscope (ThermoFisher Scientific).

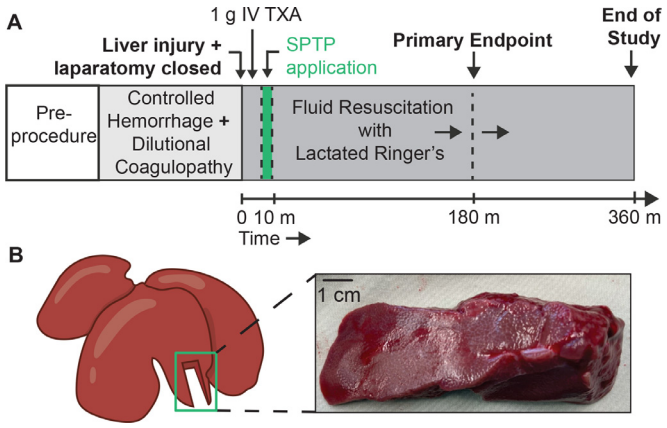

Fig. 2. Protocol of swine model of NCIAH. (A) Protocol of swine model of NCIAH. (B) Photo of a representative 10 cm x 3 cm rectangle cut out of the left medial lobe of the liver to trigger massive hemorrhage.

Statistical analysis

Statistical analysis for the swine study was performed with GraphPad Prism 8.0.1. Baseline physiological characteristics and controlled hemorrhage volumes were compared using a t-test. Percentage of animals surviving was analyzed with a Fisher's exact test. Survival curves in pigs were analyzed with Kaplan-Meier survival analysis. Mean arterial pressure, heart rate, end-tidal CO_2, and coagulation tests over time were analyzed with repeated measures analysis of variance (ANOVA). All other secondary outcomes were compared using t-tests. All values were considered statistically significant at $p<0.05$.

Results

Efficacy of SPTP spray system for managing NCIAH

Using the porcine model of NCIAH (Fig. 2), the survival of animals receiving SPTP delivered using the spray device (n=10) was compared to a control group (n=9) receiving only fluid resuscitation. Baseline physiological and blood parameters did not differ significantly between the two groups. Two animals in the SPTP group died before SPTP could be administered; these animals were excluded from the study and were not considered in the final sample size. The mean controlled hemorrhage volume before the liver injury did not differ significantly between the fluid resuscitation only and SPTP groups (330 mL ± 49 mL vs 347 mL ± 54 mL, p=0.83). Prothrombin time (PT) coagulation tests were used to assess the degree of coagulopathy. Within each group, PT showed a statistically significant increase from baseline to 30 min post-liver injury, increasing from 13.85 sec to 18.58 sec (p=0.04) in the fluid resuscitation group, and 13.40 sec to 17.41 sec (p=0.09) in the SPTP group. There were no differences in PT between groups at 30 min. Four out of nine (44%) animals in the fluid resuscitation group survived to three hours, compared to 6/10 (60%) animals receiving SPTP (p=0.66, risk ratio = 0.74). SPTP extended the median survival time from 1.6 hours (IQR 0.6 – 6.0) to 4.3 hours (IQR 1.6 – 5.9). By six hours, 3/9 (33%) animals in the fluid resuscitation group and 2/10 (20%) animals in the SPTP group sur-

Table 1
Specifications of SPTP for NCIAH in four pigs.

Ultrasound and catheter placement time	5.0 ± 2.5 min
Intervention time between positive FAST and delivery of SPTP	6.7 ± 1.7 min
Weight of device	166 g
Size of device	102 cm^3
Mass of SPTP delivered	18.5 ± 1.0 g
Thrombin dose delivered	18, 500 ± 1000 IU
Change in intra-abdominal pressure (IAP)	5.2 ± 1.8 mmHg

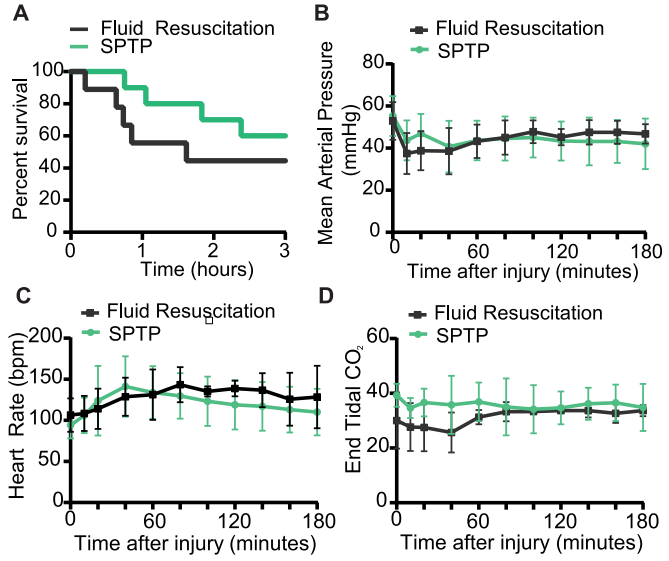

Fig. 3. SPTP may improve survival from NCIAH. (A) Kaplan-Meier survival curve of SPTP (n=10) and the fluid resuscitation only control group (n=9). (B) Mean arterial pressure over time. (C) Heart rate over time. (D) End tidal CO_2 over time.

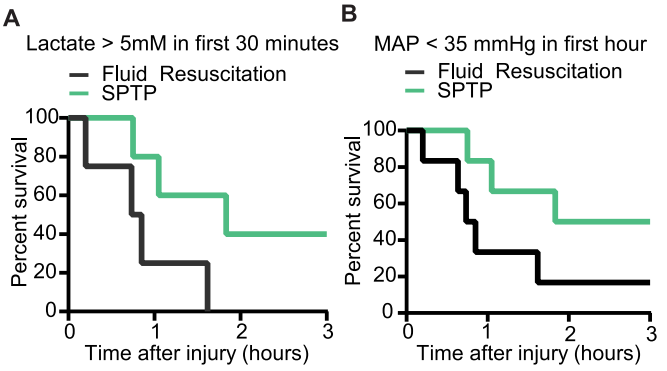

Fig. 4. Sub-population analysis shows SPTP may be capable of increasing survival in animals that have greater severity of shock or are more hemodynamically unstable. A) Survival of the sub-set of animals with serum lactate concentrations of >5 mM in the first 30 min after injury (n=5 SPTP, n=4 fluid resuscitation only). B) Survival of the sub-set of animals with a MAP of <35 mmHg in the first hour after liver injury (n=6 for both groups).

vived. Kaplan-Meier survival curve analysis after six hours did not indicate statistically significant differences in survival (p=0.87, HR=0.91) (Fig. 3A). MAP, heart rate, and $EtCO_2$ between surviving SPTP animals and control animals was not significantly different at any time points (Fig. 3B-D). There were no differences in blood coagulation parameters and other secondary outcomes among animals surviving at three hours post-injury, although there was a trend to higher lactate levels at three hours in the SPTP group possibly because animals in the fluid resuscitation group that developed high lactate did not survive (Supplementary Table 1).

Performance evaluation of the SPTP spray system

Key parameters of the spray system were measured in four pigs (Table 1). Ultrasound and catheter placement took 5.0 ± 2.5 min. Percutaneous delivery of SPTP took 6.7 ± 1.7 min. The spray system successfully delivered 18.5 ± 1.0 g of SPTP in these pigs, which corresponds with 18,500 IU of thrombin. While the target dose was 20 g, there was variability due to the use of an early stage device prototype in this study. The IAP after delivering SPTP was 5.2 ± 1.8 mmHg, versus 1.0 ± 0.33 mmHg in six pigs receiving only fluid resuscitation and not SPTP. There was an immediate increase in IAP by as much as 2 mmHg following SPTP delivery, after which only small gradual increases in IAP were observed until death. No observable adverse effects on vital signs or acute toxicity related to SPTP or the delivery device were observed during or after SPTP was applied.

Sub-group analyses of survival

Variable and longer than expected survival times may have made differences between groups harder to determine. We retrospectively determined that animals with shorter survival had high serum lactate concentrations and low mean arterial pressures. Approximately half of animals in both groups (n=5 SPTP, n=4 fluid resuscitation only) developed severely elevated serum lactate concentrations (> 5 mmol/L) within 30 minutes following liver injury, indicating hypovolemic shock. In this subpopulation, the survival at three hours was 2/5 (40%) in SPTP group and 0/4 (0%) in the fluid resuscitation group. Overall survival in this subgroup analyzed by Kaplan-Meier analysis was improved in the SPTP group (p=0.06, HR=0.33) and median survival was extended from 0.79 hours to 1.83 hours in SPTP animals (Fig. 4A). We further identified a separate sub-population with MAP of <35 mmHg within the first hour after injury (n=6 both groups). The survival at three hours was 3/6 (50%) in the SPTP group versus 1/6 (17%) in the fluid resuscitation group. Kaplan-Meier overall survival to six hours in SPTP animals was not significantly different versus the fluid resuscitation group (p=0.51, HR=0.68). However, the median survival time was extended from 0.79 hours versus 2.54 hours (Fig. 4B). In this model of NCIAH, the effects of SPTP appeared most pronounced in animals that had a severe early physiological response to uncontrolled hemorrhage. Swine are sensitive to hemodynamic manipulation, and precipitous falls in MAP are to be expected during severe hemorrhage, but a subset of animals had profound hypotension and lactic acidosis. These animals could be considered more representative of severe NCIAH, which is less survivable during delays to receiving surgery in humans.

Histopathologic analysis of tissues in swine

SPTP residue was found distributed throughout the peritoneal space including within the liver wound during necropsy, indicating

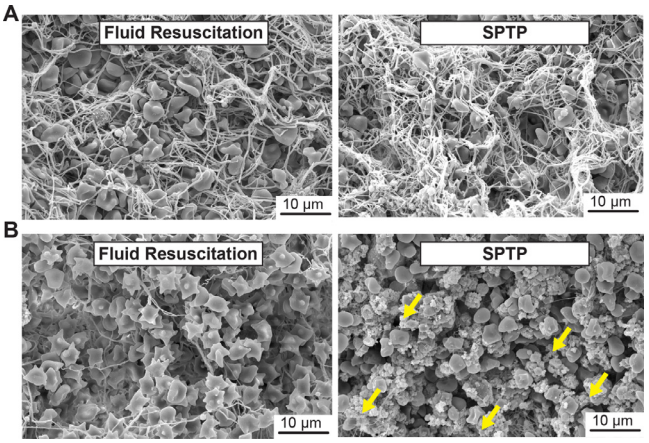

Fig. 5. Electron micrographs show that SPTP forms dense fibrin-rich clots within the abdomen. (A) Electron microscopy images showing differences in the fibrin network between fluid resuscitation and SPTP animals. (B) Electron microscopy images showing differences in red blood cell morphology between groups. Yellow arrows indicate SPTP found incorporated into clots.

that thrombin and TXA were effectively transported to the bleed site through the large hemoperitoneum. Histologic examination of liver tissues harvested from six randomly chosen animals in each group showed ischemic changes and centrilobular necrosis in 6/6 animals which received SPTP and in 5/6 which did not receive SPTP. In the same subset of animals two lungs from animals which did not receive SPTP and one from an animal which did showed accumulation of alveolar fluid and macrophages, desquamation of alveolar epithelium, and a few capillary microthrombi with focal adjacent accumulation of airspace fibrin. One kidney, from an animal that did not receive SPTP, contained patchy superficial and deep interstitial inflammation and tubular necrosis, affecting about 10% of the sampled tissue. Renal tissue sampled from animals receiving SPTP was normal. To further confirm there were no negative effects on renal function, urea and creatinine levels were measured in all animals and there were no increases from baseline in either group.

Histopathologic examination confirmed that all animals had abundant but immature clots adjacent to areas of liver injury and overlying the liver capsule. The clots consisted of closely packed red blood cells (RBCs), with scant intervening filaments of fresh fibrin and very scant collections of mature fibrin. SPTP was visible in histologic sections as basophilic, granular and partly crystalline material associated with the fibrin.

Electron microscopy analysis of intra-peritoneal blood clots

Large blood clots were also found throughout the hemoperitoneum generated by the severe liver injury. Clots were harvested and imaged using scanning electron microscopy to assess clot structure and composition. Electron micrographs from clots collected from the fluid resuscitation group displayed fibrin organized as thin fibers. RBCs that were entrapped in the fibrin network were sparsely distributed with large intercellular spaces with no cell compaction. RBCs in the fluid resuscitation group were abnormally shaped with thick protrusions, resembling crenated RBCs undergoing hyperosmotic shrinkage. In contrast, clots from animals that received SPTP were more robust and did not break down when agitated or pulled apart. Micrographs of these clots qualitatively displayed greater fibrin content and contained remnant SPTP. RBCs in clots recovered from SPTP animals did not display any abnormal conformational changes (Fig. 5A, B).

Discussion

Delivering hemostatic powder into the abdomen using a portable spray device is a feasible and safe approach to manage bleeding, which had not been demonstrated previously. There were no apparent negative effects of CO_2 from this procedure, such as CO_2 embolism [29,30]. CO_2 embolism is particularly a concern with large open veins in this model, and animals were monitored for symptoms such as sudden hypotension, tachycardia, or cardiac arrest. Increased heart rates were observed in both groups following the liver injury, which was likely due to low blood pressure. Increases in IAP of 20 mmHg or higher are known to decrease cardiac output [31]. Although cardiac output was not measured in this study, the IAP in all animals receiving SPTP did not exceed 10 mmHg, which is below pressures routinely used in laparoscopy [32]. At these low pressures, the SPTP spray system is also unlikely to produce adverse pulmonary effects. However, pulmonary function was not monitored, as all animals were mechanically ventilated and ventilator peak pressures were not measured. The safe IAP increase by the SPTP spray system was achieved through rapid prototyping of the spray device, after earlier designs increased IAP by 15-20 mmHg in swine. High intra-abdominal pressures of >20mmHg can slow bleeding [33,34] but increase the risk of developing abdominal compartment syndrome [35,36]. It is unlikely that the increase in survival in SPTP animals is due to an effect of IAP on bleeding, but additional experiments are needed.

In NCIAH where the source of the bleeding is known, injecting hemostatic powders directly at the bleed site would be highly advantageous, but often infeasible due to risks of perforating intra-abdominal structures and the inability of powders to overcome pooling blood which blocks access to the damaged vessels or organs. SPTP is a highly hemostatic self-dispersing powder that has improved survival and reduced blood loss in multiple animal models of severe hemorrhage without adverse effects [17–21]. Delivering SPTP into a hemoperitoneum results in the self-dispersion of hemostatic agents within the abdomen to reach bleed sites that could be several centimetres away. This is particularly promising for the management of blunt trauma, where the source of the bleeding can be unknown or multitudinous, but SPTP may be promising for penetrating trauma as well, due to its proven effectiveness in large vessel injuries [18–21]. To deliver hemostatic agents within the abdomen, SPTP self-disperses by generating CO_2. The CO_2 could additionally apply light pressure to the injury to help slow bleeding. CO_2 formation also augments hemostasis through the creation of bubbles in pooled blood, and these gas-liquid interfaces may promote the localization and activation of coagulation proteins [37,38]. The high local concentrations of thrombin and calcium likely explain how SPTP was incorporated into robust clots that had higher fibrin content and which were not easily pulled apart. There were no ‘barbed ends’ on fibrin fibers, which are indicative of ongoing fibrinolysis, [39] observed in the fibrin structures in clots from either group of animals, which is consistent with the administration of intravenous TXA in our model. This suggests that the higher fibrin content in abdominal clots formed in the SPTP animals is solely the result of increased conversion of fibrinogen to fibrin by thrombin. Additionally, the RBCs incorporated into SPTP clots appeared “healthier” than those in clots from control animals, which warrants further research into potential causes for this effect.

No signs of acute thromboembolic complications were observed in swine in this study. Histopathologic changes associated with ischemia and hypotension were identified among the swine, which was expected because of the severity of trauma sustained. No adverse histopathologic changes attributable to SPTP or signs of thrombosis were identified in swine upon inspection of the liver, kidneys and the lungs, and there were no differences between

groups in measured concentrations of D-dimers. This safety profile of SPTP is consistent with previous animal studies demonstrating that SPTP is safe when applied directly to large open vessels such as the femoral and carotid arteries, and also when injected intravenously [17–21]. The majority of SPTP delivered into the abdomen is expected to dissolve in blood, as SPTP is converted to CO_2 within minutes in blood, and any remnant SPTP is expected to safely degrade within days to weeks, as TXA is absorbed and cleared, and $CaCO_3$ is biodegradable [40,41]. Future studies will determine the ideal dose of SPTP for NCIAH and evaluate the long-term safety of the systemic absorption of the components of SPTP from the peritoneal space.

Extending the first "Golden Hour" following injury is critical to increase overall survival from NCIAH.[42] Current devices that act as bridges to surgery, such as REBOA and abdominal aortic and junctional tourniquet (AAJT), are associated with complications that include distal ischemia and abdominal compartment syndrome if placed for more than 1-2 hours, [43,44] which restricts their widespread use. New strategies, such as partial REBOA, [45,46] were recently approved by the US Food and Drug Administration (FDA) and Health Canada, but questions surrounding their technical feasibility remain for the prehospital setting. Although survival at the Golden Hour was not an outcome which was defined prior to the initiation of the study, it is an important consideration given its clinical relevance. Animals receiving fluid resuscitation alone had 55% survival at one hour whereas animals receiving SPTP had 80% survival at one hour, which, extrapolating to humans, could represent a 25% increase in the number of casualties surviving the "Golden Hour" and reaching surgery and long-term recovery. Furthermore, a greater percentage of animals survived to three hours post injury, and median survival times in animals administered SPTP increased more than three-fold compared to animals that received fluid resuscitation only. Although the differences in survival between groups did not reach statistical significance at these sample sizes, the results highlight the promise of SPTP in temporizing NCIAH until surgery is possible.

As an ultrasound guided procedure which uses basic non-surgical medical techniques, this intervention is accessible to medics and physicians and does not require a surgeon's skillset [47–50]. Physicians that resuscitate casualties near the point-of-injury are typically trained to perform paracentesis and similar procedures for placing catheters and tubes into free fluid within the torso, which will reduce the training requirements for using SPTP. Advanced medics may also be trained to perform this procedure. This is in contrast to the training requirements and technical skillset required to perform REBOA [51]. Similarly, foams such as ResQFoam require a laparotomy to deploy, which commits soldiers to surgery for its removal, and which is a challenging task in the prehospital environment [52]. Continued development of the SPTP intervention will improve the design of the delivery device to minimize the flow rate of exogenous CO_2 into the abdomen; this will completely eliminate the increase in IAP and reduce the risk of any pneumoperitoneum-associated complications such as CO_2 embolism. The design modifications will also likely decrease the time to deliver SPTP to $<$ 1 minute, which will make SPTP easier to deploy.

A limitation of this study was variability in survival, severity of shock, and degree of early hemodynamic decompensation. However, most animals rapidly became critically hypovolemic and their lactate levels rapidly increased, indicating that the model mimics severe NCIAH in humans and is appropriate for testing new interventions. Though pigs are considered the gold standard for modeling human hemorrhage, further studies are required to generalize these results to scenarios with different hemodynamic manipulations. The location and type of liver injury chosen was more survivable than expected even with fluid resuscitation treatment alone, and animals were particularly resilient. Closure of the laparotomy and the shifting and pressure put on the liver by other organs may also have contributed to creating tamponade on the liver bleed. Lastly, the SPTP spray system was deployed minutes after injury in this model, which differs from situations with delays to treatment that may hinder SPTP's efficacy, such as extensive clotted blood in the abdomen which could limit the dispersion of SPTP.

Conclusion

NCIAH continues to be a major problem despite enormous efforts. Here, we demonstrated proof-of-concept of a new minimally invasive procedure which could represent an additional tool for managing NCIAH. The SPTP spray system was well-tolerated and appeared useful for improving outcomes, although there was no statistically significant difference in survival between groups in this study. Further studies testing the SPTP spray system are warranted, and will fully determine the potential utility of this approach.

Declaration of Conflicts of Interest and Sources of Funding

C.J.K., M.F.C., N.A., and J.R.B. are involved in commercialization activities for self-propelling hemostatic powder. A.B. is an active serving member of the Canadian Armed Forces.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2022.01.024.

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