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Self-expanding foam injected into the peritoneal space improves survival in a model of complex pelvic fracture and retroperitoneal exsanguination

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ABSTRACT

Background Mortality for patients with pelvic fracture with hemorrhagic shock ranges from 21% to 57%. ResQFoam administered intra-abdominally has previously been shown to provide a survival benefit in large-animal models of abdominal exsanguination. It also significantly decreased mortality in models of retroperitoneal hemorrhage with complex pelvic fracture when deployed in the preperitoneal space. We hypothesized that percutaneously administered ResQFoam into the abdominal cavity could decrease mortality in exsanguinating pelvic hemorrhage.

Methods Using non-coagulopathic Yorkshire swine, the injury model consisted of a unilateral, closed-cavity retroperitoneal vascular hemorrhage (with intraperitoneal communication) combined with a complex pelvic fracture. After the injury, animals received fluid resuscitation alone (control, n=14), fluid resuscitation with ResQFoam deployed in the preperitoneal pelvic space (n=10), or fluid resuscitation with ResQFoam deployed intra-abdominally (n=10). Hemodynamic monitoring was continued for 3 hours or until death.

Results Intra-abdominal and preperitoneal use of ResQFoam provided a similar significant survival benefit compared with controls. The median survival times for the intra-abdominal and preperitoneal ResQFoam groups were 87 and 124 min, respectively, compared with 17 min for the control group (p=0.008 and 0.002, respectively). The survival rate at 3 hours was 40% for both ResQFoam groups compared with 0% in controls (p=0.020). There was no significant difference in the median survival time or overall survival curves between the two ResQFoam groups (p=0.734 and p=0.975, respectively). Both ResQFoam groups stabilized mean arterial pressure and significantly reduced hemorrhage rate. The average hemorrhage rate in control animals was 4.9±4.6 g/kg/min compared with 0.6±0.6 g/kg/min and 0.5±0.5 g/kg/min in the intra-abdominal (p=0.008) and preperitoneal (p=0.002) ResQFoam groups, respectively.

Conclusions Similar survival benefit and hemorrhage control were achieved with ResQFoam in the treatment of exsanguinating pelvic hemorrhage with complex pelvic fracture whether it was administered preperitoneally or intra-abdominally. Thus, ResQFoam can be administered intra-abdominally to treat either abdominal or pelvic hemorrhage.

Level of evidence Not applicable (animal study).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ ResQFoam is a hemostatic intervention originally developed as a treatment option for non-compressible abdominal hemorrhage. Recently, ResQFoam was shown to be a safe and effective intervention for lethal pelvic hemorrhage in swine when deployed in the preperitoneal cavity space.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that ResQFoam can be a safe and effective intervention for lethal pelvic hemorrhage when deployed intra-abdominally.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Intra-abdominal deployment of ResQFoam has the potential to be an effective intervention for abdominopelvic hemorrhage.

BACKGROUND

Despite advances in management over the last several decades, the mortality for patients with pelvic fractures who present with hemorrhagic shock is estimated to be between 21% and 60%.[1–5] Management of this patient population is particularly challenging due to massive non-compressible hemorrhage in the pelvis that occurs along with other bony and soft tissue injuries. The available interventions to control pelvic hemorrhage are angiographic embolization, preperitoneal packing (PPP), and zone 3 resuscitative endovascular balloon occlusion of the aorta (REBOA). However, there is no universal agreement regarding which of these tools should be used, and guidelines vary widely. It is well known that achieving hemostasis as early as possible following injury is critical to improve survival rates for trauma patients who are in hemorrhagic shock.[6 7] In the hospital setting, implementation of these therapies is often protracted, with a reported median time of 45 and 130 min after hospital admission until patients undergo PPP or angiographic embolization treatment, respectively.[8] Incredibly, one study reported even longer delays where 70% of patients did not undergo angiographic embolization until 120–240 min after hospital admission; the delays were significantly associated with increased mortality.[9] Of the three

available interventions, neither angiographic embolization nor PPP can be used in the prehospital setting. While prehospital application of REBOA has been reported, it is not standard practice and is challenging to implement; furthermore, clinical guidelines state that there should be expedient access to surgical/endovascular control of hemorrhage if REBOA is used (even with zone 3 occlusion for pelvic hemorrhage), which is incongruous with relatively long prehospital transport times.[10 11]

ResQFoam is an in situ forming, self-expanding polymer foam designed to control severe intra-abdominal hemorrhage. The device consists of two liquid phase components that are mixed and injected within the abdomen and apply internal pressure, creating a tamponade effect. The system was developed to be amenable for application in the prehospital environment by paramedic-level users with appropriate training.[12] Furthermore, ResQFoam has been found to be safe (e.g., no evidence of abdominal compartment syndrome) and effective for a minimum of 3 hours of use.[13 14] ResQFoam is currently an investigational product with Breakthrough Device designation from the Food and Drug Administration.

Recently, the potential benefit of ResQFoam was evaluated in two highly lethal, closed-cavity, mixed arteriovenous pelvic hemorrhage injury models in swine.[15] The study demonstrated the feasibility of ResQFoam to be deployed within the preperitoneal pelvic space, leading to a significant survival benefit relative to controls. The results also highlighted that ResQFoam can provide effective hemostasis in other spaces besides the abdominal cavity.

While successful in animals, clinical translation of ResQFoam deployment within the preperitoneal pelvic cavity of humans would require additional investigation, particularly regarding subsequent foam removal and safety. In contrast, the logistics of ResQFoam deployment within the abdominal cavity have been extensively studied and established, including in recently deceased human subjects[16]; consequently, if intra-abdominal deployment of ResQFoam is effective in the treatment of pelvic hemorrhage, translation of the technology for this indication becomes more straightforward. Thus, the objective of the current study was to evaluate the life-saving potential of ResQFoam when deployed intra-abdominally in an otherwise lethal, pelvic hemorrhage animal model.

METHODS

Animal preparation and instrumentation

Healthy, female Yorkshire swine (*Sus scrofa domestica*) 41–50 kg with no prior procedures were used. Experiments were performed after obtaining approval from the Institutional Animal Care and Use Committee and in accordance with the Animal Welfare Act. Animals were acclimated for 2 days after acquisition. The Animal Research: Reporting of In Vivo Experiments guideline was used to ensure proper reporting of methods, results, and discussion. The initial preparation and instrumentation of animals have been described in detail elsewhere.[17] Briefly, animals received general endotracheal anesthesia and were instrumented for hemodynamic and intra-abdominal pressure monitoring.

Lethal, unilateral, closed-cavity retroperitoneal hemorrhage injury with bony injury

A lethal, unilateral, closed-cavity retroperitoneal hemorrhage injury with bony injury has been described.[15] We used the same model in this study to evaluate the performance of intra-abdominal ResQFoam deployment on survival. Additionally, two additional control animals were randomly enrolled in the study to confirm the lethality of the model and consistency with historical results; these animals were combined with 12 control animals from the previous study to make a control group with 14 animals. In total, comparisons were made between n=10 animals in the intra-abdominal ResQFoam group of this study, n=10 animals in the preperitoneal ResQFoam group of the previous study, and n=14 control animals.

Please refer to King *et al*.[15] for details on animal instrumentation, vascular and bony injury setup, and other model details. Animals were subdivided into two groups (known by research personnel): intra-abdominal ResQFoam or control. Control animals received fluid resuscitation only. Foam deployment in the intra-abdominal ResQFoam group was initiated 1 min after vascular injury. ResQFoam was percutaneously delivered through a nozzle that was inserted into the abdominal space via an incision made above the umbilicus. A 100 mL dose of ResQFoam was used, which is a standard preclinical volume that was optimized based on efficacy and safety from a prior study.[17] After vascular injury, animals were monitored for 3 hours or until death, defined as end-tidal carbondioxide <8 mm Hg or mean arterial pressure (MAP) <15 mm Hg, whichever came first. At the conclusion of the experiment, animals were euthanized, and hemorrhage was quantified as previously described.[15]

Statistical analysis

A sample size of at least nine animals per group was required to detect a survival rate difference of greater than 50% with a one-sided significance level of 0.05 and 80% power. This analysis was based on a log-rank test for Kaplan-Meier survival probability. The primary endpoint was survival through 3 hours. Survival over time was presented using Kaplan-Meier curves; log-rank tests were used to compare between groups. Survival data was censored at 3 hours and summarized using median values. Fisher's exact tests were used to determine differences for categorical variables, which were summarized as counts and percentages. Continuous variables were summarized using mean±SD and compared using analysis of variance or summarized using the median with quartiles and compared using Kruskal-Wallis tests. Pairwise comparisons between groups were made when these statistical tests indicated significance across the three groups (with Tukey adjustment for multiple testing). Statistical significance was two-sided and defined as $p<0.05$. Analysis was performed using SAS V.9.3 (The SAS Institute, Cary, North Carolina, USA).

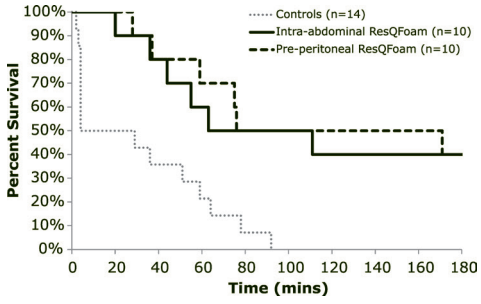

Figure 1 Kaplan-Meier survival curve showing that intra-abdominal ResQFoam intervention resulted in a significant survival benefit relative to the control group that is equivalent to preperitoneal ResQFoam intervention. Log-rank tests were used to compare the survival curves. p=0.005 for preperitoneal ResQFoam versus controls; p=0.009 for intra-abdominal ResQFoam versus controls; p=0.975 for preperitoneal ResQFoam versus intra-abdominal ResQFoam.

Table 1 Primary and secondary endpoints

Parameter	Control (n=14)	Intra-abdominal ResQFoam (n=10)	P value (vs control)	Preperitoneal ResQFoam (n=10)	P value (vs control)	P value (intra-abdominal vs preperitoneal ResQFoam)
Survival at 1 hour	3/14 (21%)	6/10 (60%)	0.092	7/10 (70%)	0.035	1.000
Survival at 2 hours	0/10 (0%)	4/10 (40%)	0.020	5/10 (50%)	0.006	1.000
Survival at 3 hours	0/10 (0%)	4/10 (40%)	0.020	4/10 (40%)	0.020	1.000
Survival time, min	17 (4–60)	87 (42–180)	0.008	124 (59–180)	0.002	0.734
Hemorrhage, g	1748±353	1388±407	0.042	1292±355	0.017	0.722
Hemorrhage, g/kg*	37.4±6.5	29.8±10.6	–	29.1±9.0	–	–
Hemorrhage, g/kg/min	4.9±4.6	0.6±0.6	0.008	0.5±0.5	0.002	0.611
Baseline lactate (mmol/L)*	1.2±0.6	1.3±0.4	–	1.2±0.2	–	–
Final lactate (mmol/L)*	9.2±3.7†	10.0±4.5	–	7.6±4.3	–	–
Baseline hematocrit (%)*	26±2	25±1	–	26±1	–	–
Final hematocrit (%)*	25±3	29±4	–	26±6	–	–
Baseline platelets ($\times10^9$/L)*	303±58	263±60	–	305±44	–	–
Final platelets ($\times10^9$/L)*	243±62	216±46	–	240±30	–	–

Median values are reported with quartiles for survival time. Mean values±SD are presented for all other values. Survival rate was analyzed using Fisher's exact test. Pair-wise comparisons between groups were only made when analysis of variance, Kruskal-Wallis test, or Fisher's Exact test indicated a significant difference across the three groups at a 0.05 level of significance.
*Indicates no significant difference between groups for the parameter.
†Based on an n=7 due to lack of final blood sampling as a result of animals quickly expiring within 5 min of injury.

RESULTS

A total of 12 animals were enrolled in the study (e.g., none excluded due to inconsistent injury), with n=10 animals allocated to the intra-abdominal ResQFoam group and n=2 animals allocated to the control group. Following the Principles of Humane Animal Experimentation in reducing the number of animals for research, we combined the n=2 control animals in this study with an n=12 control animals from previous work using the same injury model. The n=2 control animals confirmed the lethality of the injury model; the Kaplan-Meier survival curve shows 100% lethality for the control group with a median survival time of 17 min (figure 1). Survival times ranged from 3 to 92 min; 7 out of the 12 control animals (58%) expired within 5 min of injury and never received fluid resuscitation.

Intra-abdominal ResQFoam administration resulted in a significant survival benefit compared with the control group, as shown in the Kaplan-Meier survival curve (figure 1). The median survival time, survival rate at discrete time points, and hemodynamic endpoints are summarized in table 1. The median survival time was 87 versus 17 min in the intra-abdominal ResQFoam and control groups, respectively (p=0.008). The survival rate at 1 hour was 60% versus 21% in the ResQFoam and control groups, respectively (p=0.092); the survival rate at 3 hours was 40% versus 0% in the intra-abdominal ResQFoam and control groups, respectively (p=0.020). Finally, intra-abdominal ResQFoam intervention significantly reduced hemorrhage from 4.9±4.6 g/kg/min in control animals to 0.6±0.6 g/kg/min (p=0.008).

The survival benefit provided by intra-abdominal ResQFoam deployment in this study was compared with that when ResQFoam was deployed within the preperitoneal pelvic space (preperitoneal ResQFoam) using the same lethal, polytrauma hemorrhage injury model.[15] There was no significant difference in survival benefit between the two groups as shown by the Kaplan-Meier survival curve (p=0.950) (figure 1). As described in table 1, the median survival time was 87 versus 124 min in the intra-abdominal and preperitoneal ResQFoam groups, respectively (p=0.734). The survival rate at 1 hour was 60% and 70% for the intra-abdominal and preperitoneal ResQFoam groups, respectively (p=1.000); the survival rate at 3 hours was 40% for both groups (p=1.000). The hemorrhage rate for both groups was also similar and not statistically different. Finally, there were no statistical differences observed across groups regarding final concentrations of lactate, hematocrit, or platelets. Images of ResQFoam at necropsy and subsequently after removal for the two groups are shown in figure 2. In the intra-abdominal ResQFoam group, the foam was removed as a single block; no material crossed through the peritoneal window and into the preperitoneal cavity. In the preperitoneal ResQFoam group, the foam had expanded from the preperitoneal cavity space and into the abdominal cavity, resulting in its removal as two pieces.

The impact of intra-abdominal ResQFoam intervention on hemodynamic stability relative to the control group is shown in figure 3. At baseline, the MAP in both groups was similar to one another, and both exhibited a severe drop to an average of 35±7 mm Hg at 1 min following vascular injury initiation. Over the course of 1–5 min postinjury, the MAP in the control group continued to steadily decline, reaching <15 mm Hg in seven animals. In contrast, MAP in the intra-abdominal ResQFoam group decreased only to 29±8 mm Hg. This data reflects the positive impact that ResQFoam alone has on hemodynamic stabilization. Once fluid resuscitation was initiated, MAP of the control group increased to an average peak of 37 mm Hg at approximately 18 min and thereafter rapidly declined to <15 mmHg. In contrast, MAP for the intra-abdominal ResQFoam group peaked at approximately 50 mm Hg during fluid resuscitation and thereafter was maintained at approximately 45 mm Hg in surviving animals. The hemodynamic stabilization was similar between the intra-abdominal and preperitoneal ResQFoam groups.

DISCUSSION

This investigation demonstrated that intra-abdominal ResQFoam administration improves survival in a polytrauma model of massive, exsanguinating, retroperitoneal arteriovenous pelvic hemorrhage. The results of this study augment those of a previous study, where efficacy was established using the same injury model where ResQFoam was injected directly within the preperitoneal pelvic space.[15] A comparison of the results shows

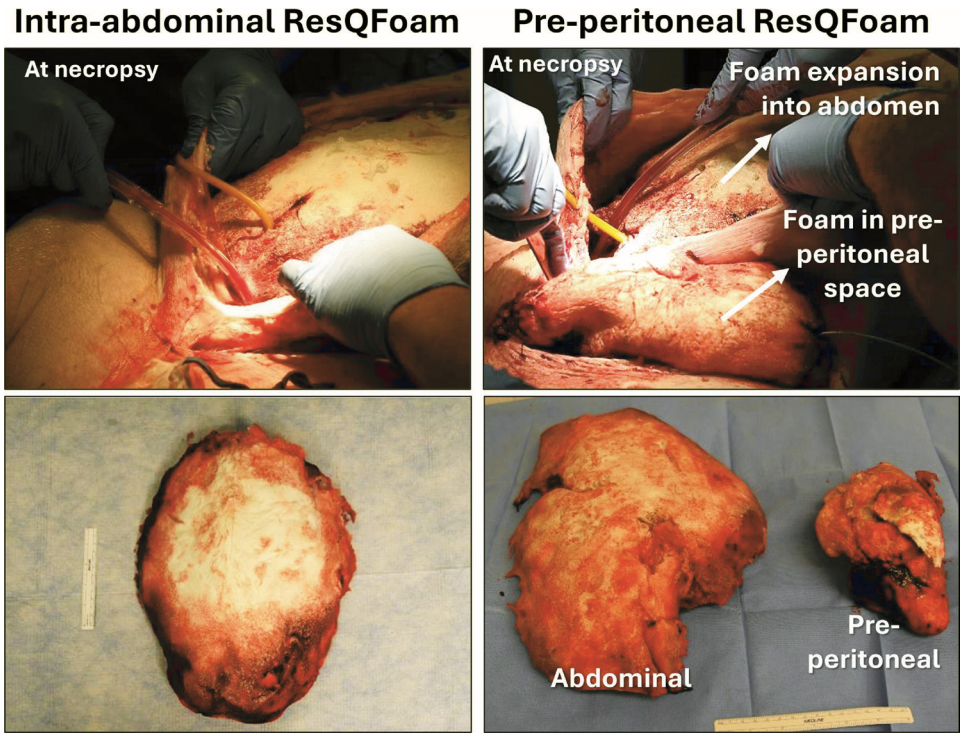

Figure 2 Digital photographs showing ResQFoam at necropsy and after removal. The foam was removed as a single block in the intra-abdominal ResQFoam group, whereas it was removed as two separate pieces in the preperitoneal ResQFoam group.

that both approaches provide similarly equivalent outcomes regarding survival benefit, hemodynamic stabilization, and hemorrhage reduction. It was noted that the median survival time in the intra-abdominal ResQFoam group was approximately 30% lower than the preperitoneal ResQFoam group, but this result was not significant (87 min vs 124 min, p=0.734). Additional studies with higher power would need to be conducted to determine whether this is a true difference (with the hypothesis being that foam expansion occurring at the site of injury enhances hemorrhage control through material contact).

The efficacy of ResQFoam, when deployed intra-abdominally, has now been established in three models of different bleeding scenarios, including the present highly lethal, high-pressure, high-flow arterio-venous pelvic hemorrhage. The other two lethal models were a low-pressure, high-flow hepatoportal venous and a high-pressure, high-flow arterial intra-abdominal hemorrhage.[18 19] Evaluation in multiple preclinical models solidifies the life-saving potential of ResQFoam and supports testing in a clinical setting. These results are particularly important since hemorrhage due to traumatic injuries does not always occur in a single location; approximately 12% of potentially preventable hemorrhage deaths are associated with bleeding in both the abdominal and pelvic cavities.[20] From a product development perspective, the advancement of ResQFoam for treatment

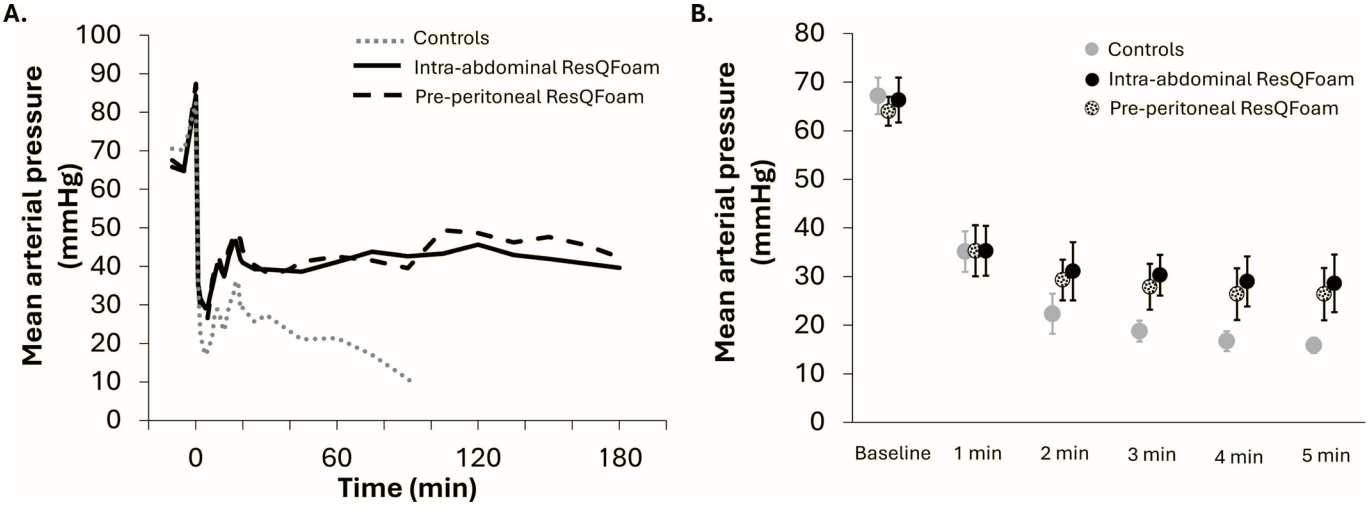

Figure 3 Mean arterial pressure curves. Panel A depicts mean values of mean arterial pressure as a function of time from surviving animals throughout the study duration. Panel B depicts interval plots of the mean arterial pressure for each group within the first 5 min after injury and prior to fluid resuscitation. Mean arterial pressure rapidly decreases following injury, resulting in eventual exsanguination within the control group. Intra-abdominal and preperitoneal ResQFoam interventions both stabilize mean arterial pressure relative to controls.

specifically for a pelvic hemorrhage indication is simplified and leverages the extensive work that has been performed for intra-abdominal deployment for ResQFoam (ie, delivery, removal, dose, biocompatibility, and safety).[13 14 16 17] The next step is a clinical study of ResQFoam for the treatment of abdominopelvic hemorrhage in a hospital setting. Patient selection and diagnosis of non-compressible hemorrhage have been described elsewhere.[12] Briefly, we propose the appropriate population be identified by the coexistence of physiology consistent with severe hemorrhagic shock (eg, hemodynamic instability), coupled with confirmation of bleeding in the abdomen (eg, positive FAST or positive diagnostic peritoneal lavage).

The main limitation of this study was the lack of true randomization of animals between groups (with the exception of two control animals) since data for the control and preperitoneal ResQFoam groups were generated in a prior study. We believe that the data can be comparable since the animal model was the same across all groups and lethality was confirmed with the concurrent controls. Furthermore, utilization of a side-wall vascular injury (through insertion and removal of a catheter) resulted in a consistent model with respect to hemodynamic instability; indeed, the MAPs at 1 min postinjury across the three groups were all 35±7 mm Hg ($p=0.998$), which indicates a severe and rapid rate of exsanguination. There was no correlation between survival time and MAP at 1 min in any group.

Another limitation of the study was an intervention at 1 min postinjury, which is not representative of a real-life scenario. The intervention was performed at 1 min due to the severe, lethal nature of the model. At 1 min, animals were already in a physiological state of severe hemorrhagic shock. By 4 min, MAP in the control animals had decreased to 16±3 mm Hg, with 50% of animals (7 out of 14) meeting the death criteria. Thus, setting an intervention time beyond 4 min would have been impractical. For this study, we believe that the physiological state of the animal at the time of intervention is more important than the timing of the intervention postinjury. In the clinical scenario, it is expected that ResQFoam will be deployed to patients with a range of blood pressures, depending on the severity of their bleeding and injury.[21] Our results indicate that ResQFoam would be efficacious even when delivered to a patient who is in a state of severe hemorrhagic shock.

Finally, a third limitation is that hemorrhage quantification may not be entirely accurate due to an inability to completely aspirate blood from all tissue surfaces. However, we believe that the data is precise given that consistent methods were applied by the same operators and that any inaccuracy would apply systematically across all groups. Furthermore, any residual blood would be relatively insignificant compared with the difference in hemorrhage between the two ResQFoam groups and the control animals, which was statistically a large effect size ($\eta^2=0.17$).

In conclusion, similar survival benefits and control of hemorrhage were obtained with ResQFoam in the treatment of exsanguinating pelvic hemorrhage, whether it was deployed intra-abdominally or within the preperitoneal pelvic space. These results indicate that ResQFoam can be deployed intra-abdominally to treat both abdominal and pelvic hemorrhage.

Contributors QPP, JOH, AEE, AIE, MJD, SG, and MF performed the data collection and contributed to study design. QPP, JOH, DRK, and US contributed to the literature search, study design, data interpretation, and writing. DRK is the guarantor.

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