CONTROL OF HEMORRHAGE – BELLY FOAM

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Noncompressible abdominal bleeding, particularly due to large vascular injury, represents a significant unmet medical need on the battlefield and in civilian trauma. This type of injury accounts for approximately 50% of potentially survivable battlefield casualties (1-4). A survey of the Department of Defense Trauma Registry (DoDTR) found that within this population, over 80% of lethal abdominal vascular injuries involved major arterial hemorrhage (5, 6). Reviews of the National Trauma Data Bank have found similarities in anatomic causes of noncompressible hemorrhage between military and civilian populations, and that such injuries were associated with high mortality (7, 8). There are currently no available pre-hospital treatments other than rapid transport to definitive surgical care, and many patients die en route to this intervention (2).

To address this need, an abdominal hemorrhage control intervention has been engineered for use in the prehospital environment. An in situ forming poly(urea)urethane polymer has been developed that can spread throughout a closed abdominal cavity in the presence of hemorrhage and create conformal contact with sites of injury. The system functions by dynamically mixing and injecting two liquid phases: a polyol phase and an isocyanate phase. Upon mixing, two reactions are triggered. First, a blowing reaction expands the material by approximately 30-fold its initial volume, ultimately allowing conformal contact of the polymer with the injured surfaces. Second, a gelling reaction transitions the material from liquid to a solid poly(urea)urethane polymer foam capable of providing resistance to intra-abdominal blood loss.

We investigated the dose-dependent efficacy of a self-expanding polyurethane foam in a lethal, non-compressible, grade V hepato-portal injury model of massive venous exsanguination (9). Results suggested that foam treatment promoted survival (in a dose-dependent fashion), while the control group (fluid resuscitation alone) exsanguinated rapidly. The largest dose (120 mL)
offered the best survival advantage, while the smallest dose (64 mL) conferred less survival advantage than 120 mL, but was still better than control animals.
Following injury, hemodynamics rapidly improved and this allowed animals to survive for three hours.

Vital signs by foam dose. (A) mean arterial pressure, (B) cardiac output, (C) intraabdominal pressure.
This model tested a low-pressure, high-flow, venous bleeding scenario (9, 10). A limitation of this model, however, was high volume crystalloid resuscitation and ventilation with 100% oxygen (11), features inconsistent with current Tactical Combat Casualty Care (TCCC) guidelines (12). This initial work specifically tested the durability of hemostasis under conditions known to promote bleeding.

Next, a model of massive, non-compressible arterial exsanguination (high-pressure, high flow arterial bleeding) was created while incorporating TCCC resuscitation guidelines (13) in order to address limitations in the original hepato-portal injury model. This model utilized a lethal, closed-abdomen iliac artery transection injury with low volume/hypotensive resuscitation with room air ventilation in additional to foam treatment. The two most promising foam doses were selected for testing in this model based upon the liver injury work. Both doses offered a survival advantage.
After injury, experimental animals received foam at two different initial volumes, or “treatment doses”: 100 mL or 120 mL. Control animals received fluid resuscitation alone. A significant survival benefit was noted with both foam doses compared to control. Similar to the liver injury model, hemodynamics rapidly improved after foam therapy.
Mean arterial pressure (A), cardiac output (B), and intraabdominal pressure (C) following foam deployment in an arterial injury model. Intraabdominal pressure over the first 30 minutes is shown in (D). MAP and CO decreased following injury, resulting in exsanguination within the control group. Foam administration resulted in a transient increase in IAP and recovery of vital signs.

At both doses, foam administration resulted in a decrease in hemorrhage rate relative to the control group. The median hemorrhage volume was 0.27 g/kg/min in the 120mL group and 0.23 g/kg/min in the 100 mL group, compared to 1.4 g/kg/min in the control group.
Foam was removed from the abdomen at three hours as a single block, in less than two minutes in both models. The foam material did not adhere to tissues, although in certain cases abdominal organs were encapsulated by the material and freed manually. Additionally, gross pathology of all abdominal organs after foam deployment was unremarkable except for the observation of focal, ecchymotic lesions on small and large bowel (9, 14), which would require repair or resection for long term survival.

Despite differences in animal models, the normalized hemorrhage rate was similar in this study to our previous model. At the 100 mL dose, the median hemorrhage rate was 0.23 g/kg/min in the iliac artery model, and 0.37g/kg/min in the liver injury model. These results support our hypothesis that foam administration slows bleeding to a sublethal rate, promoting survival relative to the control group.
There is no universally-accepted animal model for the testing of pre-hospital interventions. Therefore, it is important to test hemostatic devices over a broad range of bleeding scenarios (15), especially high-pressure, high-flow arterial hemorrhage where death is swift and certain without intervention. Multiple testing scenarios further reduce the risk of false positive findings based on assumptions inherent to animal models. For example, the Hemcon chitosan dressing for external injuries was found to be effective against venous bleeding (16), but results were inconclusive in mixed (arterial and venous) (17) and arterial bleeding (18, 19). Likewise, QuikClot Zeolite granules were effective in venous and mixed bleeding (17, 20), but were not as effective in high-pressure, high-flow arterial bleeding scenarios (18).

Despite a demonstration of efficacy in two different exsanguination models, acute testing identified several potential safety risks associated with foam use. Specifically, we observed that use of the foam, while life-saving, resulted in transient intra-abdominal hypertension raising the potential concern of end-organ injury from abdominal compartment syndrome. Second, we observed focal ecchymotic lesions in the small and large intestine, associated with regions closely apposed to the polymer. Third, we noted that the abdominal cavity temperature increased marginally following foam deployment due to the exothermic nature of the polymerization reaction. Finally, the long-term impact of exposure to some foam remnants of an *in situ* curing poly(urea)urethane required investigation. Modulation of initial dose may mitigate each of these complications, but we expect all efficacious doses to be associated with some safety risk.
To answer these questions, a 28 day survival study was conducted. A non-lethal closed-cavity splenic transection injury was created. Ten minutes after injury, animals received hemostatic foam at different doses of 100 mL and 120 mL. Controls received fluid resuscitation alone. The foam was removed after three hours, and animals were monitored over a 28-day period. Focal ecchymotic bowel lesions were identified, as expected. Bowel was repaired via imbrication with 2-0 vicryl suture or resection and end-to-end anastomosis at the discretion of the surgeon. All animals survived 28 days. No complications were observed. Neurologic status was normal by modified swine veterinary coma score. Elevated leukocyte counts were not observed. In all groups, blood laboratory assays did not demonstrate any end-organ failure and were similar in foam groups relative to the control group (Figure 4). Weight gain was not different between the 100mL and control groups (12±3.2 kg vs 13±3.6, respectively); the 120mL group did not gain as much weight (6.6± 4.9 kg, p<0.05 vs controls) due to ileus and poor PO intake.

Histologic sampling of abdominal organs at 28 days did not reveal any evidence of adverse toxicology, pathology, or embolization of remnants. The liver, spleen, bladder, small bowel, spiral colon, and peritoneum of all groups were similar to the control group (data not shown). Of note, no tissues had any evidence of thermal-related coagulative necrosis or sequelae of healed necrosis. Foam particles were found on serosal surfaces and were encapsulated by a fibro-cellular reaction not associated with granulomatous tissue. The inflammatory response to foam particles was similar to that of biodegradable suture.
In a separate series of tests, foam biocompatibility was evaluated according to ISO-10993 standards for the evaluation of medical device biocompatibility. Foam samples satisfied the requirements for all ISO-10993 assays. The material was found to be non-cytotoxic, non-sensitizing, non-irritating, not acutely toxic, non-pyrogenic, and non-genotoxic. The foam did not have an unacceptable local inflammatory response following intramuscular implantation for 30 days.

While further translational research is required, one can imagine this intervention providing a prehospital “hemostatic bridge” for severely bleeding casualties, who would otherwise bleed to death in the field, such that they can arrive alive to a surgical treatment facility. One can also imagine this technology being useful at smaller, community hospitals where emergent laparotomy capabilities are not available. A community surgeon could “foam” a patient to provide hemostasis and transfer to a Level I center for definitive care…for a patient who would have otherwise bled to death on the way.

REFERENCES


