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Percutaneous damage control with self-expanding foam: pre-hospital rescue from abdominal exsanguination

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Non-compressible intra-abdominal hemorrhage results in significant morbidity and mortality in contemporary trauma medicine. Regrettably, many deaths from non-compressible hemorrhage are attributable to potentially survivable injuries. A self-expanding polyurethane foam has been developed for rapid, percutaneous damage control of exsanguinating abdominal hemorrhage, for patients not expected to survive to definitive surgical care. Foam intervention creates a temporary, commensal, hemostatic environment within the abdominal cavity. This tropism away from exsanguination physiology creates a hemostatic bridge such that the patient may reach definitive surgical intervention. This review article summarizes the existing literature characterizing the safety and efficacy of this intervention, along with a study in recently deceased patients that enables dose translation from animal models to human beings.

Keywords
Non-compressible hemorrhage, bleeding, foam, pre-hospital, abdominal

Introduction

In severely bleeding trauma patients, rapid hemorrhage control is critical to ensure survival. Pre-hospital control of exsanguinating hemorrhage could potentially prevent a majority of trauma deaths in the pre-hospital environment[1–3] as well as the 40% of hemorrhage-related deaths that occur after hospital presentation.[4,5]

Emergent damage control laparotomy remains the standard of care for life-threatening intra-abdominal bleeding.[6,7] Over 20,000 patients suffered injuries resulting in non-compressible truncal hemorrhage between 2007 and 2009 in Level I trauma centers in the United States. The mortality rate was 44.6% in this population,[8] highlighting the need for rapid hemorrhage control interventions whenever surgical care is not immediately available, or even within hospitals during preparation and transfer to surgery. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emerging therapy for this purpose, but this technique requires endovascular access and is associated with a variety of problematic complications.[9–12]

To address the unmet need, a self-expanding polyurethane foam has been developed for the temporary treatment of massive, non-compressible abdominal exsanguination[13–22] in the pre-hospital environment. The intervention consists of two liquid precursors contained in a percutaneous delivery system. Following diagnosis and abdominal access using standard minimally invasive surgical techniques, the liquids are injected as a mixture. *In situ*, the material reacts and expands, spreading throughout the abdominal cavity and creating a commensal relationship to injured organs. The foam expands approximately 35-fold relative to the initial volume, creating a tamponade effect to slow or stop blood loss and salvage patients who would otherwise die. This temporary pro-survival tropism allows patients to be rescued from exsanguination and survive to definitive surgical care. The material is intended to be removed at the time of definitive damage control

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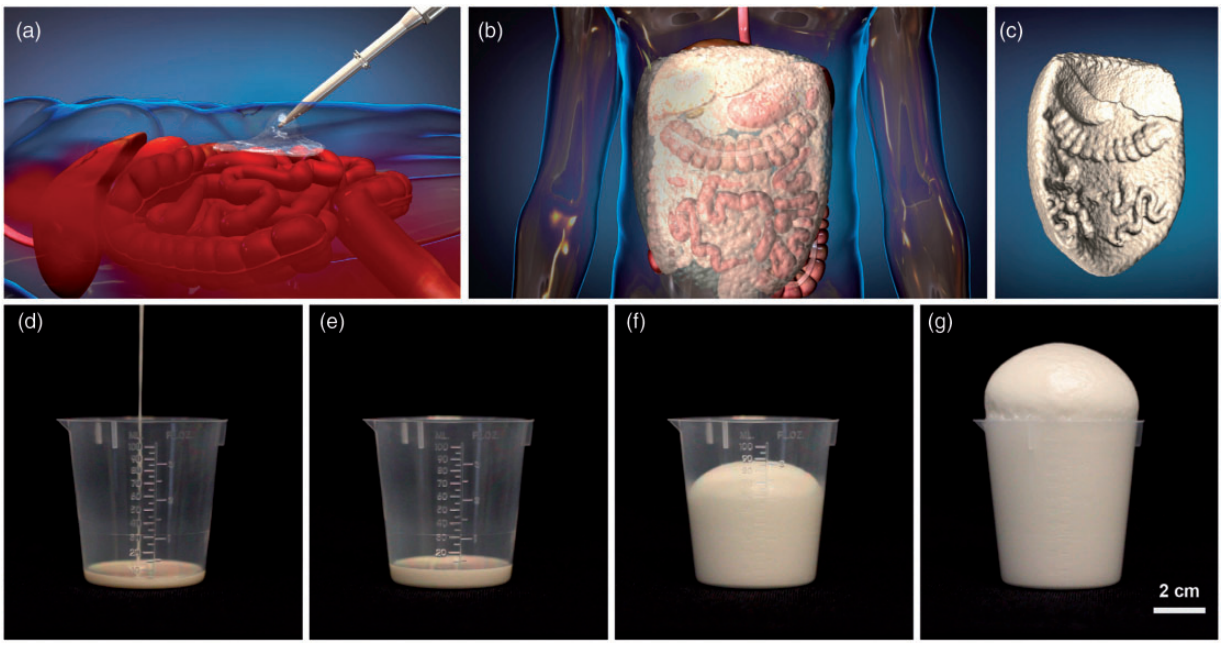

Figure 1. Conceptual rending of self-expanding foam: (a) Foam is deployed as a mixed liquid and reacts in situ to expand throughout the abdominal cavity (b); foam is removed at the time of definitive surgery (c). Foam expansion *in vitro* is shown in a 100 mL beaker (d–g). Adapted from Rago et al.[28].

laparotomy. The foam, in a temporal fashion over approximately 90 seconds, is shown schematically (panels A, B, and C) and *in vitro* (panels D–G) in Figure 1. The goal of this review is to summarize the large body of preclinical data (over 600 live animal experiments) as well as available human dose-translation science supporting the favorable risk-benefit profile of self-expanding foam for rescue from abdominal exsanguination.

Data included in this review

Ten publications have described the efficacy, safety, and dose translation of exsanguination rescue with percutaneous foam damage control.[13–22] Results from those studies are reviewed, with particular discussion centered around bleeding that would otherwise result in death before surgical intervention is possible.

Results and discussion

Efficacy studies

The development of self-expanding hemostatic foams necessitated design of multiple novel animal models to evaluate efficacy. Prior to our initial work, there were no existing, reproducible, non-coagulopathic, closed-cavity models of lethal abdominal hemorrhage. We developed two models: a low pressure, high flow hepatoportal injury model and a high pressure, high flow iliac artery transection model.[14,15] In both models, a midline laparotomy was used for strategic placement of cutting wires within the abdomen; the cavity was closed, and severe, non-compressible bleeding was subsequently induced by distracting the wires. These injuries were lethal when animals were given only fluid resuscitation, the current standard of care in the pre-hospital environment for impending traumatic arrest from bleeding.[14,15]

In the hepatoportal injury model, the liver and portal vein were severely lacerated. Foam was injected percutaneously through a 12 mm trocar (placed in the midline, half the distance between the xyphoid and pubic symphysis) into the abdomen at varying doses, 10 minutes after injury, and compared with a control group receiving fluid resuscitation alone.[17] After injury, all animals were profoundly hypotensive and nearing traumatic arrest. Animals were monitored for 3 hours or until the time of death, followed by foam explantation. Foam conformed commensally to abdominal anatomy but was easily removed. Survival was dose dependent, but all doses demonstrated significant pro-survival tropism relative to controls at 3 hours (120 mL: 90%, 100 mL: 72%, 85 mL: 33%, 64 mL: 17% vs. Control: 8%, $p < 0.05$). A representative Kaplan–Meier curve is shown in Figure 2a for the 100 mL dose. Hemorrhage rate was also reduced in all groups relative to the control ($p < 0.05$), between 2-fold and 10-fold at the lowest and highest doses, respectively. Injury and fluid resuscitation alone resulted in

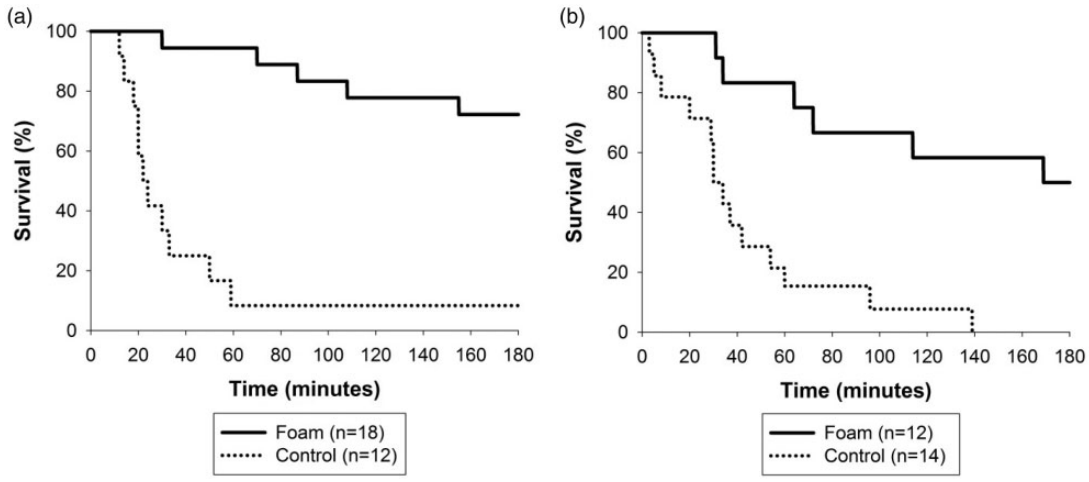

Figure 2. *In vivo* foam performance at the 100 mL swine dose. In severe liver (a) and iliac artery (b) injury models in swine, foam treatment (solid lines) resulted in a significant survival benefit relative to control groups (broken lines). Adapted from Rago et al.[17,19]

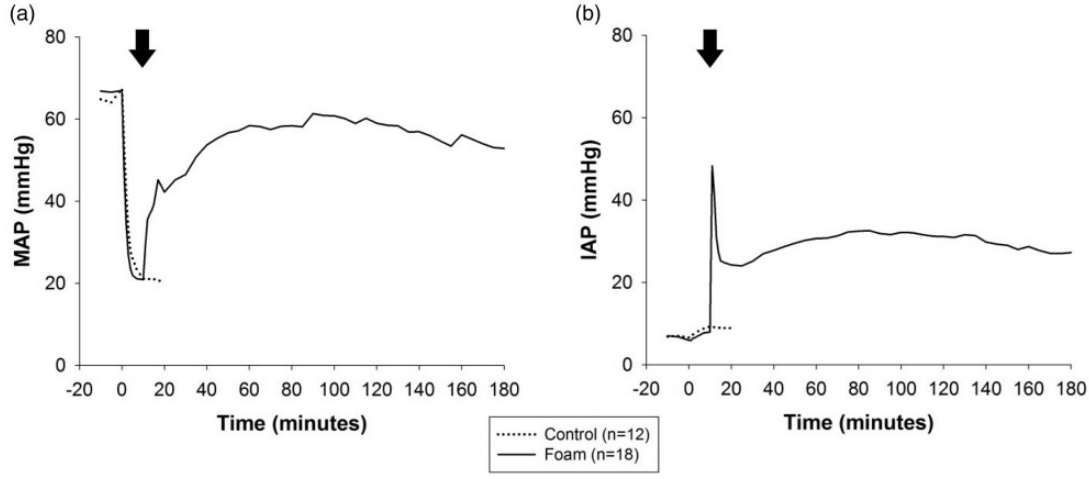

Figure 3. Mean arterial pressure (a) and intra-abdominal pressure (b) in the Grade V Liver injury model. Injury is associated with rapid, massive hypotension. Foam deployment at 10 minutes (shown with the black arrow) results in a transient increase in IAP and restoration of MAP. Adapted from Rago et al.[17]

massive hypotension and rapid exsanguination in the control group.

Two effective foam doses (100 mL, $n = 12$ and 120 mL, $n = 13$) were selected and tested in the iliac artery transection model and compared with a control group ($n = 14$).[19] Iliac artery transection resulted in profound hypotension and near traumatic arrest before intervention. Median survival time was 135 and 175 minutes for the 120 and 100 mL doses, respectively, compared with 32 minutes in the control group ($p < 0.001$). A representative Kaplan–Meier curve is shown in Figure 2b for the 100 mL dose. Foam administration resulted in an immediate, persistent improvement in mean arterial pressure and a transient increase in intra-abdominal pressure. The median hemorrhage rate was 0.27 g/kg per minute in the 120 mL group and 0.23 g/kg per minute in the 100 mL group, compared with 1.4 g/kg per minute in the control group ($p = 0.003$ and 0.006, respectively).[19]

In both hepatoportal and iliac injury models, arterial pressure was restored with foam treatment (Figure 3) resulting in tropism towards pro-survival physiology and subsequent rescue from exsanguination. Concurrently, we observed a rapid, transient, and dose dependent increase in intra-abdominal pressure associated with foam expansion, which was well-tolerated by experimental animals (17). This transient increase in intra-abdominal pressure was subsequently examined in safety studies.

Safety studies

Although efficacy studies demonstrated the ability of foam to rescue animals from exsanguination, these experiments did not establish safety beyond a 3-hour experimental time frame. To assess potential toxicity, biocompatibility, and compartment-syndrome risks, several chronic survival studies were conducted following foam administration.[18,20] A closed cavity splenic injury was performed in swine, and foam treatment was administered at multiple doses, 10 minutes after injury. Foam was explanted after 3 hours, animals were recovered and monitored for 28 or 90 days.

Foam animals were compared with a control group with injury alone. Treatment with, and subsequent explantation of foam, did not adversely impact long-term survival at doses less than or equal to 120 mL (120 mL, $n=6$ and 100 mL, $n=16$; control, $n=9$). As previously documented in acute hemorrhage control studies, foam treatment resulted in focal, dose-dependent ecchymotic bowel damage.[17] These lesions were repaired without consequence in nearly all foam treatment animals.[18,20] One animal developed a persistent postoperative ileus and was euthanized and replaced in the study. The incidence of complications associated with bowel repair not different from clinically observed rates.[23–27]

Beyond the bowel complications noted, all animals survived to the study endpoints and there were no differences in renal or hepatic function, serum chemistries, or semi-quantitative one-month abdominal adhesion scores between foam groups and the control.[18,20] Compartment syndrome was not observed. Histologic analysis demonstrated no effect of transient temperature changes and that tiny foam remnant particles (average particle size, 2.2 ± 4.6 mm^3) were associated with a fibrotic capsule and mild inflammation, less than that of standard degradable suture reaction.[20] Results were consistent between 28 and 90 days, with no evidence of late complications.[18]

The safety biocompatibility of self-expanding foams is supported through a series of tests according to ISO-10993 standards for the evaluation of medical devices. In these tests, the foam material was conditioned in liquid extraction vehicles at elevated temperatures. These extraction vehicles were subsequently tested in a range of *in vitro* and *in vivo* assays. Based on these 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 or 90 days.[20]

Secondary studies supporting efficacy in clinical use scenarios

After establishing the baseline safety and effectiveness of self-expanding foams in exsanguinating animal models, secondary studies of factors relevant to initial human use of foam therapy were conducted.[21] All testing was conducted in the hepatoportal injury model. First, foam performance was evaluated following delivery from a robust, hand-operated delivery system (Figure 4; $n=12$). This delivery system was designed to enable use in the pre-hospital environment in a ruggedized format that does not require batteries, external power, or adjunctive equipment. Foam administration with this system improved survival relative to the control group (67% vs. 7%, $p=0.006$), reduced hemorrhage rate (0.48 ± 0.41 vs. 3.1 ± 1.2 g/kg/min, $p<0.0001$), and demonstrated consistent performance with our first generation, bulky delivery device use in initial efficacy studies.[21]

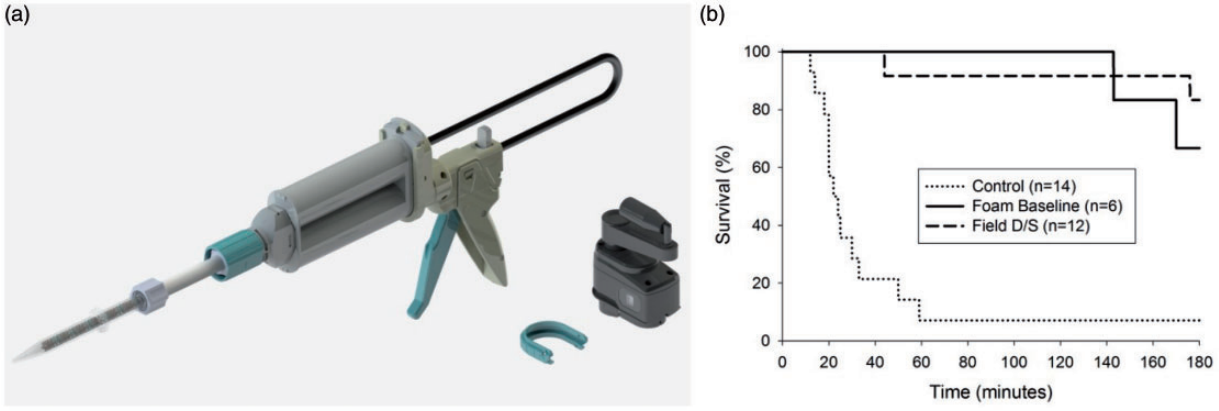

Figure 4. A robust, hand-operated delivery device was designed to enable pre-hospital use (a). This device resulted in a survival benefit and reduction in blood loss when tested in a preclinical hepatoportal injury model, similar to the first-generation delivery system (b). Adapted from Rago et al.[21]

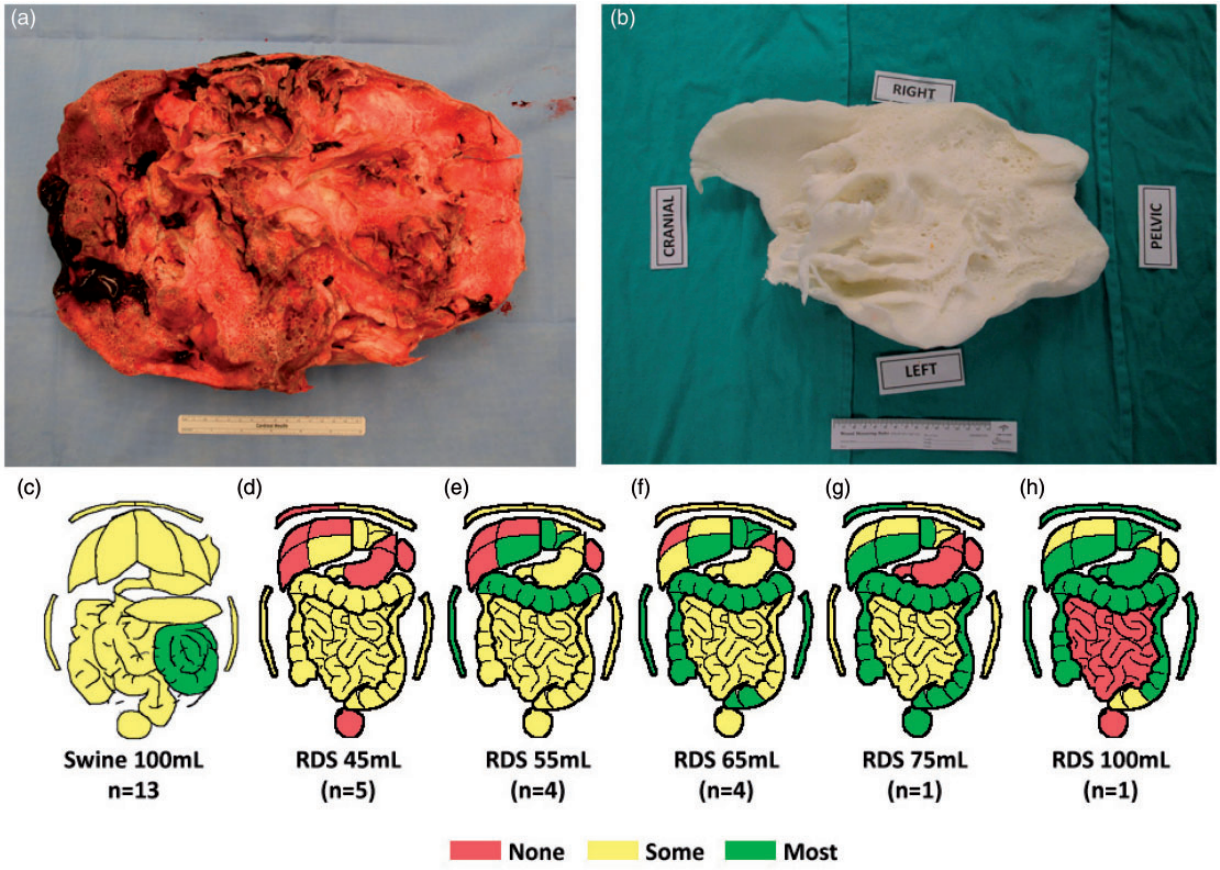

Figure 5. Representative image of foam appearance following testing in swine (a) and recently deceased human subjects (b). Average foam-organ contact following deployment in recently deceased human subjects is depicted graphically (red = none, yellow = some, green = most). Swine data are shown for reference (c); recently deceased study data are shown in d–h. Adapted from Mesar et al.[16]

In follow-on studies, foam components were conditioned to operational temperature extremes (10°C or 50°C) immediately prior to deployment ($n = 6$ per group). Additionally, foam was conditioned to simulate a one year shelf life ($n = 6$). In both studies, foam treatment significantly improved survival and reduced hemorrhage rate relative to the control group. Deployment of foam conditioned to temperature extremes did not result in hypothermia, hyperthermia, or thermal injury (21). Finally, the hepatoportal injury model was modified to include full-thickness injuries in the diaphragm. Foam treatment, in the presence of diaphragm injuries, resulted in a survival benefit relative to the control group at 1 hour (67% vs. 10%, $p = 0.036$, Figure 2) but not 3 hours ($p = 0.072$).[22] Based on these findings it was concluded that hemothorax should be evacuated prior to foam administration.[22]

Translational research for human use

Differences in comparative anatomy suggest that the appropriate swine dose cannot be directly translated to humans. To approximate the human dose, an engineering analysis was conducted comparing the abdominal pressure–volume relationship as measured by gas insufflation in swine to that of humans. These data were used to create a scaling factor between the size of the swine and human abdominal cavities. This analysis suggested the human starting dose for a first-in-class, multicenter prospective study of foam performance in recently deceased human patients with informed consent.[16] The recently deceased population was utilized to test foam in human anatomy with representative tissue compliance, at appropriate temperature, with no risk to patient safety. It was hypothesized that recently deceased subjects could be utilized as a translational model to select an appropriate human foam dose, leveraging intra-abdominal pressure and commensal foam-organ contact, as surrogate endpoints for safety and effectiveness.[16]

Twenty one recently deceased humans ranging in age from 20 to 92 years and BMI 18 to 39 kg/m^2 were enrolled in the study.[16] Foam was administered 146 ± 34 minutes after death. Three subjects were

screen failures, and three subjects were excluded from analysis due to experimental errors. Change in intra-abdominal pressure and semiquantitative organ contact were used as surrogates to compare findings between humans and swine. About 45, 55, and 65 mL doses resulted in peak pressures of 37 ± 20, 28 ± 8.1, and 33 ± 20 mmHg, respectively, within the acceptable range established in swine studies. About 75 and 100 mL foam deployments exceeded acceptable pressures defined in swine.[16] In swine studies, foam was distributed throughout the abdomen, with some contact of the diaphragm, paracolic gutters, and bladder. In recently deceased subjects, contact with the liver, large bowel, and diaphragm improved with increasing dose (Figure 5). Among doses with acceptable intra-abdominal pressure, organ contact was optimal at the 65 mL foam dose and was similar to that observed in swine. About 65 mL was selected as the appropriate dose for foam intervention in bleeding human patients.[16] The use of recently deceased human subjects was a novel and critical translational step toward the safe and effective use of foam to rescue patients from exsanguinating hemorrhage.

Conclusion

Presurgical non-compressible abdominal exsanguination remains a clinical problem without an available solution. The large volume of preclinical data supports a favorable risk-benefit profile for self-expanding foam treatment. Foam therapy creates a pro-survival tropism that provides temporary hemostasis and allows rescue from abdominal exsanguination, salvaging those who would otherwise die before surgical intervention.

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Declaration of conflicting interests

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