A Reversible Hydrogel Dressing for Hemostasis and Wound Management

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Disclosures:

Introduction: In some scenarios such as trauma sustained in military actions or in rural or wilderness settings, emergent surgical care may not be available for hours or even days after the event. Emergent care at the scene of injury is essential for optimal outcomes, as uncontrolled bleeding can result in death, and contamination can result in infection. Current methods for acute hemorrhage control as instructed in Advanced Trauma and Life Support (ATLS) training include pressure tamponade - which may not control bleeding adequately in abdominal wounds - and tourniquet application or compression dressings in extremity wounds, which may result in ischemia of uninjured tissues. Furthermore, direct pressure is difficult to apply unless performed by a caregiver, who may be unavailable in scenarios of military action, or when the number of casualties exceeds the number of responders. Despite the recent development of dressings impregnated with human clotting agents, organic compounds and minerals, there is no clinical standard for the field application of hemostatic agents to abdominal or extremity wounds at the scene of injury. None of the available dressings has been successful at reliably and effectively controlling severe bleeding for any significant period of time under field conditions. Additionally, none of these materials has the capability to dissolve and gradually re-expose a complex wound as all require mechanical debridement for removal.

To address these scenarios, we hypothesize that a reversible hydrogel based dressing can be used as a portable system for emergent hemostasis of abdominal and extremity wounds. This dressing could potentially provide better and faster accessibility to initial care at the scene of injury than present standards. To that end, we I) designed and optimized a reversible dendritic thioester hydrogel used to induce immediate adhesive and occlusion hemostasis; and II) evaluated the resistance, endurance and reversibility of the hydrogel matrix system in an ex-vivo soft tissue model of simulated bleeding pressures.

Methods: Reversible Dendritic Thioester Hydrogel Dressing: The hydrogel dressing is a dissolvable dendritic thioester hydrogel based on thiol-thioester exchange. The thiol end groups of the dendrimer react with a PEG(NHS)2 macromer to form an adhesive hydrogel at the injury site. The hydrogel can be dissolved after its application with biocompatible thiolate solutions.

Ex-vivo Testing System: In order to assess the effectiveness of the hydrogel dressing in withstanding physiologic pressures, we built a testing apparatus to measure flow and pressure within a reservoir lined with skin harvested from Fisher rats (Figure 1). Data from both the flow (FLR-1007, Omega Engineering - Stamford, CT) and pressure (PX-309, Omega Engineering - Stamford, CT) sensors were collected per second into a data logger (DAQPRO-5300, Omega Engineering - Stamford, CT). By feeding normal saline into the system in a continuous or pulsatile manner, we were able to simulate venous or arterial bleeding pressures, respectively.

Resistance to failure: Incisions with 2.5 mm (n=6) and 4.1 mm (n=8) diameters were made on intact rat skin and then covered with 90 µL and 200 µL of the hydrogel dressing, respectively. After 10 minutes, pressure within the system was gradually increased until the dressing failed (noted by a steep decrease in pressure and visible leakage of saline through the wound) or
until the pressure within the system reached 250 mmHg (upper limit for the study).

**Endurance:** We assessed the capacity of the hydrogel to withstand high steady pressures for a period of 24 hours. Incisions with 2.5 mm (n=3) and 4.1 mm (n=3) diameters were made on intact rat skin and then covered with 90 µL and 200 µL of the hydrogel dressing, respectively. After 10 minutes, pressure within the system was gradually increased until it reached 200 mmHg, at which point we clamped the lines and recorded pressure values every second for a 24 hour period. As a control, we tested a group made up of intact skin (ie, without incisions) (n=3). We also assessed the capacity of the hydrogel to withstand fluctuating (“arterial”) pressures for a period of 24 hours. Similarly, 2.5 mm (n=3) and 4.1 mm (n=3) incisions were made on intact rat skin and then covered with 90 µL and 200 µL of the hydrogel dressing, respectively. After 10 minutes, the system was subjected to fluctuating pressures (between 100 and 180 mmHg) with a rate of 200 rpm using a peristaltic pump (Masterflex 75-7553, Cole Parmer Instrument Co. - Chicago, IL).

Following the above experiments we assessed the reversibility of the hydrogel dressing by dismounting the used tissue and submerging it in a cysteine solution.

**Results:** When used to cover 2.5 mm incisions, the hydrogel withstood pressures > 250 mmHg (maximum value measured by the sensor) without any signs of failure or leakage in all tests. In 4.1 mm incisions, the hydrogel dressing withstood an average pressure of 228.26 ± 28.15 mmHg. There were no observable fluid leaks or signs of failure of the hydrogel dressing during the 24 hour period of high, steady pressure. Due to the elastic and porous properties of rat skin, there was a pressure drop in all the systems (20.68 ± 2.8% in the 2.5 mm incision group; 40.15 ± 7.62% in the 4.1 mm incision group; and 24.36 ± 5.2% in the control group) after 24 hours. However, there were no statistical differences between the three groups when hourly drop rates were compared using repeated measures ANOVA with a Huynh-Feldt epsilon (p = 0.25) (Figure 2).

![Figure 2: Hydrogel endurance - Hourly drop rate of pressure in the three experimental groups (red - 2.5 mm; green - 4.1 mm; blue - control) under high, steady pressure.](image)

There were no observable fluid leaks, signs of failure of the hydrogel dressing or pressure drops in the system during the 24 hour period of high, fluctuating pressure (100/180 mmHg, 200 rpm) in neither group (2.5 mm and 4.1 mm incisions). Complete dissolution of the hydrogel dressing occurred after a 25 minute exposure to the thiolate solution in all the experiments.

**Discussion:** Our hydrogel dressing is able to adhere to ex-vivo tissues and withstand pressures well above the human physiologic range, especially in trauma scenarios where hypovolemia usually results in arterial hypotension. Furthermore, the dressing has proven to resist high, continuous and fluctuating pressures for periods of at least 24 hours without signs of failure. These characteristics make the hydrogel dressing a suitable agent for hemostasis of severe venous and arterial bleeding in field scenarios. The hydrogel dressing has the additional advantage of being easily dissolved with biocompatible thiolate solutions, allowing trauma surgeons to gradually remove the dressing without mechanical debridement, thus reducing blood loss and soft tissue damage.

**Significance:** Our objective is to develop a hydrogel dressing for emergent abdominal and extremity wound management that will provide critical initial care beyond present standards. Unlike currently available wound dressings, the hydrogel will provide non-clotting cascade dependent hemostasis. A unique characteristic of our hydrogel dressing is its capability to be gradually
dissolved after its application, so that the wound area can be re-exposed in a controlled manner to allow for definitive surgical care in an operative setting. This will reduce blood loss and the subsequent need for transfusions, thus avoiding the logistical difficulties associated with blood bank availability and depletion.

Acknowledgments:
References:

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