Influence of Celox Rapid's Mode of Action Under Normal and Compromised Blood Conditions

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There have been significant advancements in scientific understanding and technology with respect to bleeding and hemostasis. Despite this, trauma remains a leading cause of human morbidity and mortality.[1] Assessment of the types of trauma reveals that hemorrhage is the main cause of preventable death in both combat and civilian trauma situations.[2–4] To complicate this scenario, approximately 25% of severely injured patients have an established trauma-induced coagulopathy on arrival at the emergency department, a phenomenon associated with an increased rate of early and late mortality.

Trauma-induced coagulopathy is caused by several factors associated with the trauma itself as well as certain interventions undertaken[5–7] and results in a disposition toward a slower coagulation process. Although trauma-induced coagulopathy is multifactorial, it is definitively the most important issue for the management of severe trauma patients.[8] Rapid hemorrhage control is one of the key areas of support within the medic's arsenal of devices. While the tourniquet is the first line of treatment in the majority of injuries, areas requiring compressible hemorrhage control not amenable to limb tourniquet use or as an adjunct to tourniquet removal remain strategic management. These areas require a hemostatic product.

A review of the extensive literature on hemorrhage control highlights that not all scenarios are the same, and the patient's condition, both externally and internally, plays a significant part of the efficacy of the treatment provided. One of the key goals, therefore, is to ensure that the treatment is as effective as possible in all situations to provide the optimal chance of survival.

When assessing junctional hemostatic devices, the prominent and most reported product types split into two categories: those that primarily affect and promote the body's natural clotting cascade and those that primarily absorb the excess fluid and gel and create a robust gel-like plug. Both product categories play a significant part in aiding the survival of the patient following injury.

The purpose of this paper is to review the role a proprietary chitosan-based hemostatic agent (Celox Rapid), which absorbs fluid to create a gel-like plug, potentially plays in managing and controlling bleeding in normal and compromised conditions. The US Department of Defence's Committee on Tactical Combat Casualty Care (CoTCCC) has added Celox Gauze to its guidelines for control of hemorrhage as hemostatic agents for military-wide use. Already in use by US Special Forces, the CoTCCC decision now makes Celox available to every member of the DoD. Celox Rapid is the latest development in the Celox Gauze range of products.

Celox Rapid has been formulated to have a distinct and effective mode of action, which is designed to work independently of the clotting cascade and not be affected by any potential changes within the blood system.

The primary mode of action is a device function comprising of the formation of the gel plug to stop bleeding. Within this mode of action there are two key elements. The first element is the gelling action, the second element is the adhesive properties of the gel around the newly formed gel plug.

The first element of the primary mode of action is when the chitosan-based granules contact aqueous fluid the chitosan chains extend due to the electrostatic repulsion between the protonated amines and the solubilizing effect of the fluid. Effectively, the chitosan chains are dissolved into the fluid. Once extended, the chains form a mesh-like structure linked with both chain entanglement and a newly formed intermolecular and intramolecular hydrogen bonding network that occurs through the absorbed water molecules. The effectiveness of the hydrogen bond network is driven by the proprietary and unique chitosan formulation within Celox Rapid. This gives a gel structure that, once formed, does not easily dissolve in or absorb further fluid. This is due to the chitosan chains now being in a low energy state compared with the initial globular form and the new hydrogen bonding network being in place. Laboratory testing demonstrates the ability of the proprietary chitosan-based granules to absorb fluids from the body, which includes whole blood, anticoagulant-impregnated blood, and diluted anticoagulant-impregnated blood at a range of temperatures (4.3° C–55° C, including the normal condition of 37° C and hypothermic condition of 35° C), within 60 seconds.[10] The gel created in all of these scenarios has very similar properties in terms of viscosity, density, and robustness, indicating that the product efficacies are similar irrespective of the profile of the blood.

The second element of the mode of action is the bioadhesive nature of the product. This is achieved in two ways. The primary method is via the bioadhesive within the formulation.

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Due to the chemical nature, the bioadhesive readily swells in water, providing a large adhesive surface for maximum contact with the mucin (the glycoprotein predominant in the mucous layer), resulting in adhesion of the bioadhesive to the mucin while maintaining an adhesive force between the tissue surface and the product. This key element allows for compression to be released after 60 seconds compared with the standard protocol of care of 3 minutes.

A second aspect is the hydrogen bonding network within the chitosan matrix, which can extend to the amino acids present in the tissues, giving a degree of adhesion to the wound. This adhesion could also be caused by an electrostatic interaction between the positively charged chitosan salt and the lone pair of tissue amine groups. Laboratory studies have shown that the tissue adhesion properties of Celox Rapid are significantly higher than other products on the market[11] irrespective of the profile of the blood (i.e., whole blood or compromised blood [diluted or anticoagulated]).

Following absorption of fluids and after the creation of the robust gel, a further element of this adhesive characteristic can be observed between the gauze layers. This adhesive characteristic helps stabilize the different layers of the gauze during packing and combined with the tissue adhesion and helps hold and maintain the gel-like clot even during movement of the patient, reducing the risk of rebleeding during evacuation.

The multiple hydrogen bonding interactions throughout the gel structure, extending to the tissues, give sufficient cohesiveness to the structure of the device to effectively plug the wound and stop bleeding irrespective of the profile of the blood.

On formation of the robust gel plug around the site of bleeding, the combination of the different properties of the product and the gel plug create a conducive environment to allow the body to naturally undertake the hemostasis process, while minimizing the risk of rebleed due to movement or other forces.[12]

In in vivo models using the Institute of Surgical Research femoral artery 6mm punch model, the proprietary chitosan-based hemostatic technology in Celox Rapid was shown to work in both normal and compromised blood conditions.[12,13] These data support the findings of the in vitro testing and the relevance of the tests. The blood within these tests was diluted with Hextend (by 33%) and made hypothermic (35° C).

In a trauma environment, whereby diagnosis of any underlying complicating condition is neither practical nor currently available, speed and effectiveness of treatment are essential. Using a technology that does not depend on understanding the underlying physiology of the condition while still working effectively has the potential to save lives. Complications, prolonged treatment time, and potential rebleeds can be successfully prevented by the timely application of the proprietary chitosan-based technology within Celox Rapid. This in turn has the potential to aid in prognosis, resulting in increased probability of survival.

Disclosure

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