A New Hemostatic Agent: Initial Life-Saving Experience With Celox (Chitosan) in Cardiothoracic Surgery

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Celox (MedTrade Products Ltd, Cheshire, UK) is a proprietary preparation of chitosan, indicated for moderate to severe hemorrhage and currently used for hemostasis in the emergency and military settings. We describe its lifesaving use in 2 patients undergoing cardiothoracic surgery in which conventional techniques had failed.

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Celox (MedTrade Products Ltd, Cheshire, UK) is a proprietary preparation of chitosan, which is the term used to describe a series of polymers derived from crustacean chitin with different degrees of deacetylation (defined in terms of the percentage of primary amino groups in the polymer backbone [DD]), and average molecular weights (Mw). The DD of chitosan is usually between 70% and 95%, and the Mw is between 10 and 1,000 kDa. Changing the reaction conditions during the manufacturing process alters the DD and Mw of chitosan. Structurally, chitosan is a linear polysaccharide consisting of β (1-4)-linked 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (N-acetyl-D glucosamine) units, and it is very similar to cellulose, which is made up of β (1-4)-linked D-glucose units, and in which there are hydroxyl groups at C2 positions of the glucose rings [1].

Chitin is obtained from ecologically sound natural sources: crab-shell and shrimp-shell wastes. Chitosans have widespread applications, have been widely studied in the biomedical field, and are highly biocompatible. Celox (MedTrade Products Ltd) itself, has a Food and Drug Administration approval (ie, 501[k]), class 3 CE marking, and a North Atlantic Treaty Organization stock number as a hemostatic agent in the emergency and battlefield settings in which anecdotal reports of its use have been highly encouraging. This is supported by in vivo experimental work showing 100% effectiveness in an industry standard model of lethal groin hemorrhage in swine [2].

Previous in vitro work has shown the ability of Celox to clot heparinized blood. This has been replicated in vivo in a modification of the industry standard model of lethal haemorrhage, whereas chitosan has been shown to be effective in heparinized rabbits [3]. This seems to be effective by direct electrostatic interaction between negatively charged cell membranes of the erythrocytes and positively charged chitosan, independent of classical coagulation pathways [4]. Where chitosan has been used to close experimental carotid artery punctures in sheep, no infectious complications were seen at the wound site at up to 6 months of follow-up [5].

Case Reports

Patient 1

A 63-year-old Caucasian man (preoperatively Canadian Cardiovascular Society Angina Classification class 3, New York Heart Association class II) underwent on-pump coronary artery bypass grafting surgery. A standard dose of heparin (3 mg/kg) was given and an activated clotting time (ACT) of 550 seconds achieved prior to bypass with further heparin to maintain an ACT of greater than 600 seconds on pump. Aprotinin was not used. A left internal thoracic artery graft was placed to the left anterior descending coronary artery (LAD) and saphenous vein grafts to a further three vessels. The LAD was heavily calcified and deeply intramyocardial. Surgery was described by the operating surgeon as technically difficult, subsequent bleeding was troublesome, and the patient remained in the operating room for a prolonged period to achieve hemostasis. Heparin was reversed with Protamine and a coagulopathy treated with fresh frozen plasma, platelets, cryoprecipitate and eventually Factor VII. Eventually the chest was closed and the patient was transferred to the intensive care unit.

Further bleeding ensued and the patient was returned to the operating room, where it was apparent that bleeding continued from the intramyocardial dissection of the LAD. Conventional hemostatic agents were applied; however bleeding continued unabated. Celox was applied to the site of bleeding and pressure was applied using a gauze swab for approximately 5 minutes. On release of the swab it was clear that the bleeding had stopped. The patient's hemodynamic condition improved, the chest was rapidly re-closed, and the patient returned to the intensive care area. The overall recovery was slow due to an anterior myocardial infarct. Transesophageal echocardiographic and hemodynamic measurements suggested that this had occurred intraoperatively, prior to the application of the Celox. He subsequently recovered to be discharged home.

Patient 2

A 50-year-old Caucasian man was admitted to the emergency department, having been stabbed in the root of the right side of the neck. Available information was that the weapon was a kitchen knife, approximately measuring 15 cm long and 1.5 cm wide. On arrival he was unresponsive with an unrecordable blood pressure. A chest roentgenogram showed a right hemothorax and the chest tube drained more than 2 L of blood. He was resuscitated and emergently transferred to the operating room. A thoracotomy was performed, providing good access to the subclavian vessels. Evacuating a further 2.5 L of blood and clot exposed heavy bleeding from the apex of the thoracic cavity. It was not possible to expose the vessels clearly, and hemostasis was attempted with a number of

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pledgeted 3.0 Prolene sutures (Ethicon, Somerville, NJ) supported by liberal use of conventional hemostatic agents. Although this seemed to achieve hemostasis, continuous transfusion was required to maintain an adequate circulation. In spite of the ongoing transfusion, the patient then suffered a cardiac arrest. Resuscitation included bolused epinephrine and internal cardiac massage. The parietal pleura at the apex of the thoracic cavity were then widely opened, and extensive arterial hemorrhaging was encountered. Pressure was applied and the contents of a 35-gm pack of Celox was directly applied to the site of bleeding. Gauze swabs were placed over the Celox and strong pressure was applied for 5 minutes, by which point hemostasis was obtained. The patient immediately became hemodynamically stable. Excess material was washed out and the chest was subsequently closed. The patient was extubated the next morning, neurologically intact, and he was transferred out of the intensive care unit in the morning on postoperative day 3. His postoperative course was complicated by a myocardial infarct, management of which with low molecular weight heparins for a long period and also dual anti-platelet therapy precipitated two late re-bleeds. He subsequently underwent ligation of the subclavian artery but currently remains an inpatient with respiratory failure.

Comment

Increasing awareness of the importance of rapid control of hemorrhage in the military trauma setting has focused on methods of reducing hemorrhage at the point of injury [6]. A number of agents have been assessed for this role in the military environment. These include bandages impregnated with chitosans (eg, HemCon dressings [HemCon Inc, Portland, OR] or QuikClot zeolite powder dressings [Z-Medica, Wallingford, CT], or both) and more recently chitosan granules (Celox). The experience with HemCon (HemCon Inc) and QuikClot (Z-Medica) in experimental models has been mixed, although there is evidence that the use of HemCon bandages have been significantly beneficial on the battlefield [7]. Celox has been shown to be more effective in vivo in an experimental model of trauma, possibly due to its ease of application. The most important aspect of its use is to ensure that the Celox granules are in direct contact with the site of bleeding. Although chitosans are highly biocompatible, being composed of glucosamines, we considered it safer to remove as much excess product as was possible. Its use in the setting of major vascular injury should be considered an adjunct to, not a replacement for, surgical repair. The late ligation of the subclavian artery in the second case, almost certainly a complication of the management of his ischemic heart disease, confirms this, but it also shows how effective Celox was initially.

These are, we believe, the first two reported uses in surgery, although we are aware of previous unreported uses. In our cases, the usage of Celox seemed to have been lifesaving. Indeed the second usage, apart from being in the operating room, was almost as suggested on the packet. Given that it clots heparinized blood, it would seem sensible that future use in cardiac surgery is guided in this knowledge to apply it after the heparin has been reversed. Furthermore, care should be used in the presence of cell savers. It would seem that further studies to ascertain its role in surgery are strongly indicated.

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