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Advances in Therapy® | *Volume 24 No. 3*
May/June 2007

Hemostatic Effects of Microporous Polysaccharide Hemosphere® in a Rat Model With Severe Femoral Artery Bleeding

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ABSTRACT

An appropriate hemostatic dressing for prehospital use should lower mortality due to uncontrolled hemorrhage. In this study, the investigators explored the hemostatic effects of Microporous Polysaccharide Hemosphere® (MPH) applied in a rat model with severe femoral artery bleeding. Twelve rats were randomly assigned to MPH and control groups: The femoral artery of each rat was pierced to initiate bleeding. Then, 0.25 g MPH was poured into the bleeding site. A 200-g scale weight was placed over the bleeding site for 30 sec. At 30-sec intervals, the scale weight was removed, and hemostasis was assessed visually. After 30 sec, if the bleeding had ceased, the test was scored and checked as "passed at 30 sec." If the bleeding had not stopped, the same procedures were

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repeated a maximum of 3 times. If hemostasis could not be achieved even after the third application, the test was scored as failed. The same sequence of procedures was repeated for the control group without use of MPH and with only standard compression. Application of MPH resulted in complete control of bleeding in 2 of 6, 4 of 6, and 6 of 6 rats at 30, 60, and 90 sec, respectively. In the control group, however, hemostasis could not be achieved in all 6 rats, even at 90 sec. The difference between the 2 groups was statistically significant (*P*=.007). Application of MPH and compression with a scale weight significantly decreased the time of hemostasis in the rat model with femoral arterial bleeding.

Keywords: uncontrolled hemorrhage; hemostasis; hemorrhage control; hemostatic dressing; Microporous Polysaccharide Hemosphere

INTRODUCTION

Uncontrolled hemorrhage continues to be the leading cause of death among military personnel. It is the second leading cause of death in civilians worldwide. Bleeding also leads to blood transfusions with their inherent risk of complications, as well as significant expense, among surviving victims.

Rapid and immediate intervention provided by an on-scene first responder or by the victim himself is one of the most effective methods of reducing a patient's morbidity and mortality. During the past few years, tremendous advances have been made in the development of advanced hemostatic products that are used in traumatic bleeding. CELOX™ (Chitosan Linear Polymer) (Medtrade Biopolymers Inc., Crewe, England), Microporous Polysaccharide Hemosphere® (MPH, TraumaDEX®; Medafor, Inc., Minneapolis, Minn), HemCon Bandage® (HemCon, Inc., Portland, Ore), Rapid Deployment Hemostat® (Marine Polymer Technologies, Cambridge, Mass), QuickClot® (Z-Medica, Wallingford, Conn), American Red Cross fibrin dressing, dry fibrin sealant dressing, bovine clotting factors, acetylated poly-N-acetylglucosamine, mineral zeolite molecular sieve, poly-N-acetylglucosamine, and microporous hydrogel-forming polyacrylamide are some of the products that are already available on the market. Some are now in use in prehospital settings, emergency departments, and operating rooms.[1-8]

The ideal hemostatic dressing for prehospital use should (1) stop large vessel arterial and venous bleeding within a few minutes after it is applied to the wound; (2) provide a good outcome even after it is applied over an active bleeding site that causes pooling; (3) be ready to use, with no requirement for mixing or special preparations; (4) be simple to apply by the wounded victim, a bystander, or a medic/emergency medicine technician who has had minimal training; (5) be lightweight and durable; (6) be stable and functional at room temperature for at least 2 years and in extreme ambient temperatures (between –10°C and +55°C) for several weeks or longer; and (7) be safe to use, posing no risk of injury to the tissue to which it is applied. It must not allow transmission of bacterial or viral infection, it should be inexpensive, and it must be able to sustain hemostasis for at least several hours to permit safe evacuation of casualties to definitive care centers.[7]

MPH seems to meet many, but not all, of these requirements. It is made from purified potato starch, is formed into 30- to 100-micron spheres with a microporous surface, and is poured directly into a bleeding wound. The pores, when applied directly

onto an active bleeding wound, act to rapidly dehydrate blood and concentrate clotting proteins, red blood cells, and platelets to promote instantaneous clot formation. At the same time, the microsphere surface may promote clotting. MPH is a relatively safe and simple agent because it is bioinert; it also contains no human proteins. The product has an extended shelf life and can be applied in a 1-step process.[1,2,6,9,10]

The main goal of this study was to determine the hemostatic effects of the application of MPH and standard compression in an experimental rat model with severe femoral artery bleeding; only a limited number of studies in the literature have investigated the hemostatic effects of MPH, and the results have been controversial.[1,6,9,10] In these studies, manual compression was applied over the bleeding artery in a routine manner; however, the investigators in the present study used a different technique for the first time. Standard compression was applied over the bleeding femoral artery with the use of a 200-g scale weight.

MATERIALS AND METHODS

The study protocol was approved by the Animal Research Committee of the University of Dokuz Eylul. Twelve female Wistar rats that weighed between 200 and 400 g were used in this study. Animals were maintained on a 12-h light/dark cycle at a room temperature of 20°C to 22°C, with water and food freely available.

Anesthesia and Monitoring of Rats

Anesthesia was induced with 2% to 3% halothane in oxygen and was maintained with 1.5% halothane (in 100% O_2) delivered through a face mask during the experiment. During surgery, concentrations of end-tidal carbon dioxide and halothane were monitored with the use of a capnograph (Anesthesia Gas Monitoring 1304, Bruel and Kjaer, Naerum, Denmark). Temperature was measured with the aid of a rectal probe, which was kept stable at 37.0±0.5°C during the entire study and was controlled under guidance of feedback to the heating lamp.

Experimental Design

After the left leg was shaved, an incision was made; this was followed by blunt dissection to sufficiently expose the femoral artery/vein bundle. Bundle sheaths were then dissected for a distance of 20 to 25 mm to expose the femoral artery and vein. The femoral artery of the left hind leg was then cannulated for monitoring of arterial blood pressure and heart rate and for the drawing of arterial blood gas samples throughout the study. Afterward, animals were randomly assigned to the MPH and control groups.

MPH Group (MPH + compression) (n=6)

The right femoral artery was pierced with a 24-gauge needle, and active severe arterial bleeding was achieved. The wound was immediately covered with a gauze pad to remove excess blood. After the excess blood had been blotted, 0.25 g MPH powder (TraumaDEX®; Medafor, Inc., Minneapolis, Minn; http://www.medafor.com) was poured directly into the bleeding site, and a 200-g scale weight was placed on it for 30 sec so that a standard level of compression could be achieved. At 30-sec

intervals, the bleeding from the site was evaluated by an unaffiliated observer with a stopwatch who reported whether or not it had stopped. After 30 sec, the scale weight was removed, and hemostasis was assessed. If the bleeding had stopped, the test was scored as "passed at 30 sec." If the bleeding did not stop, the same quantity of MPH and the same amount of compression were reapplied for an additional 30 sec in a similar way. If bleeding stopped after the second application, the test was scored as "passed at 60 sec." If bleeding continued after the second application, a third and final time trial of the same procedure was repeated for an additional 30 sec. If the bleeding stopped after this trial, the test was scored as "passed at 90 sec." If hemostasis could not be achieved after the third application, the test was scored as "failed," and bleeding was stopped by means of additional compression, with ligation of the vessel performed as needed.

Control Group (compression only) (n=6)

The same sequence of experimental procedures was repeated for the control group without the use of MPH and with only standard compression. Hemostasis was assessed similarly at 30, 60, and 90 sec after compression provided by the scale weight was removed. At the end of 90 sec, animals in both groups were euthanized via inhalation of high-dose halothane.

Monitoring of Physiologic Parameters

Heart rate (HR), mean arterial pressure (MAP), and rectal temperature of the rats were recorded from the monitor (Petas® KMA 450, Petas Profesyonel Elekt, Ankara, Turkey). Partial carbon dioxide tension ($PaCO_2$), partial oxygen tension (PaO_2), pH, hemoglobin (Hb), hematocrit (Hct), serum glucose, and sodium (Na^+) levels were analyzed via arterial blood samples. Arterial blood gas measurements were evaluated with the use of a radiometer (Radiometer ABL, ABL 700 Series, Copenhagen, Denmark). These physiologic variables were monitored separately before bleeding was initiated and at 30, 60, and 90 sec.

Statistics

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS), version 10.0 for Windows (SPSS Inc., Chicago, Ill). Results were given as mean±standard deviation (SD). The Mann-Whitney *U* test was used for comparison of the 2 groups. A P value <.05 was considered statistically significant.

RESULTS

The difference between variables (MAP, HR, pH, $PaCO_2$, PaO_2, rectal temperature, glucose, and Na^+) in the 2 groups was not statistically significant (P>.05) at 0, 30, 60, and 90 sec. Hct values in the MPH group taken at 60 and 90 sec were significantly higher than those of the control group (P<.05) (Table).

In the MPH group, application of MPH resulted in complete control of bleeding in 2 of 6, 4 of 6, and 6 of 6 rats at 30, 60, and 90 sec, respectively. In the control group, however, hemostasis was not achieved in any of the rats, even after 90 sec. The difference between the 2 groups in time to hemostasis was statistically significant (P=.007). All 12 rats were alive at the end of the study.

Physiologic Variables

	Control Group	MPH Group
MAP, mm Hg		
0 sec	102±26	108±25
30 sec	112±18	119±48
60 sec	115±19	81±26
90 sec	109±17	88±17
HR, beats/min		
0 sec	310±83	326±44
30 sec	269±46	300±105
60 sec	276±41	249±111
90 sec	286±27	210±76
Hb, g/dL		
0 sec	12.3±0.5	12.2±0.7
30 sec	11.6±0.5	11.8±0.6
60 sec	11.0±0.6	11.5±0.5
90 sec	10.6±0.6	11.1±0.4
Hct, %		
0 sec	38.1±1.9	38.0±2.0
30 sec	35.2±1.4	36.6±1.2
60 sec	33.6±1.5	36.1±1.3*
90 sec	32.6±1.4	35.6±1.0*
pH		
0 sec	7.35±0.05	7.34±0.07
30 sec	7.34±0.09	7.34±0.04
60 sec	7.37±0.08	7.36±0.05
90 sec	7.34±0.10	7.37±0.11
$PaCO_2$, mm Hg		
0 sec	42±6	40±7
30 sec	44±9	42±6
60 sec	38±5	36±9
90 sec	40±7	38±8
PaO_2, mm Hg		
0 sec	125±12	134±12
30 sec	134±18	148±17
60 sec	148±11	139±19
90 sec	141±10	133±16
Temperature, °C		
0 sec	36.5±0.6	36.7±0.4
30 sec	36.4±0.3	36.6±0.2
60 sec	36.4±0.3	36.5±0.3
90 sec	36.4±0.2	36.5±0.7
Glucose, mg/dL		
0 sec	109±3	112±5
30 sec	111±4	118±7
60 sec	113±8	115±2
90 sec	121±7	124±11
Na, mmol/L		
0 sec	143±5	143±6
30 sec	149±11	152±9
60 sec	144±4	144±3
90 sec	143±5	146±8

*$P<.05$.

Values are expressed as means±standard deviation.

MAP=mean arterial pressure; HR=heart rate; Hb=hemoglobin; Hct=hematocrit; $PaCO_2$=partial carbon dioxide tension; PaO_2=partial oxygen tension; Na^+=sodium.

DISCUSSION

Application of MPH with a standard level of compression over a bleeding femoral artery significantly reduced the time to attainment of hemostasis compared with that reported for the control group. Although hemostasis was successfully achieved for all 6 rats in the MPH group, this was not possible for any of the 6 rats in the control group.

The extremities have been the most common sites of combat injury during the past century. With the evolution of body armor, fatal torso injuries have markedly decreased, although penetrating wounds to the face, groin, and pelvis still cause significant mortality. This is important because when compared with intracavitary hemorrhage, bleeding from extremity wounds is potentially controllable in the field with appropriate and prompt use of tourniquets or hemostatic dressings. The use of tourniquets is not always effective, however. Complications may result when they are used, and when proximal extremities are injured (eg, pelvis, groin, shoulder/axilla), the application of a tourniquet is often not suitable.[1,5,6,8,11] A suitable and effective hemostatic agent is needed that is endowed with the features mentioned earlier; however, no animal model has been universally accepted for comparison of the efficacy of all promising hemostatic dressings. Furthermore, data are insufficient to allow a direct comparison of these dressings through meta-analysis.

In the present study, lethal but potentially salvageable injuries occurred at anatomic locations that are unsuitable for application of a tourniquet. A review of the literature indicated that, in previous studies, pressure was applied over the bleeding artery through manual compression.[1,2,5] In an effort to determine how a standard level of pressure could be attained with the use of manual compression, the investigators modified this model by using a standard weighted mass.

Various studies undertaken to evaluate the hemostatic effects of MPH have yielded mixed results. Alam et al[1,2] created a complex groin injury in 30 swine to produce uncontrolled hemorrhage. A Rapid Deployment Hemostat Bandage and MPH, which produced promising results in less severe models, failed to offer any advantage in the current study. Thus, the investigators concluded that MPH itself appeared to be effective in accelerating hemostasis time in minor to moderate wounds, but not in wounds that involved severe hemorrhage. This is inconsistent with results reported for the present study, possibly because of differences in the animals studied. It is suggested that the criteria used to define minor and moderate bleeding should be stated to ensure that minor and moderate wounds across studies are comparable. In another group of 72 swine in the Alam study,[1] a complex groin injury was created that consisted of transection of the proximal thigh and complete division of the femoral artery and vein. HemCon Hemostat and MPH dressings both yielded better results than were attained in the control group. It is proposed that there were successful results with MPH because the artery had not been cut, and that the pressure created by the blood should have been lower in this case than would be expected otherwise. In the present study, the femoral artery was pierced with a 24-gauge needle rather than by cutting in order to achieve active bleeding.

Ereth et al[4] investigated the efficacy of MPH in a "modified bleeding time study" in 29 healthy volunteers. Application of MPH effectively accelerated the time of hemostasis in this model of bleeding in healthy adults. Investigators claimed that the use of MPH may represent an important advancement in the management of topical bleeding, and that it provides significant advantages over other hemostatic agents. It is noteworthy that results of the Ereth study are comparable with findings of the present study. The primary difference is that healthy human volunteers were used in the earlier study instead of rats. Neuffer et al[8] have suggested that MPH appears to be effective in accelerating hemostasis time in minor to moderate wounds, but not in severe ones.

MPH is available in 2- or 5-g sterile, ready-to-use, immediately applicable formulations that can be kept at between +60°C and –40°C. It is a relatively bioinert agent that is safe and simple to use; it contains no human proteins and has an extended shelf life.[1,2,5] Other features of the product are that it is easy to carry and handle, it can be applied directly to the bleeding site with no preparation, and it is superior in attaining hemostasis. The raw materials and production costs associated with MPH make it considerably less expensive than other hemostatic agents. The only known possible clinical contraindication to MPH is a history of an allergic reaction to potato starch. No reports have described this occurrence in any patient.[5,6,9]

The need for hemorrhage control is not limited to combat (military) medicine. Uncontrolled hemorrhage accounts for up to 80% of early civilian trauma deaths. The need for a hemostatic agent may be significant in many seriously injured patients including those who have experienced road accidents, disasters, occupational injuries, and so forth.[4-7,11] This type of agent may be used easily as a first-aid medication in the field, on the front lines of combat, to stop bleeding in military personnel; it may also be used by emergency medical staff to stop bleeding and/or to keep the wound stable until the patient is transferred to the emergency department. With the use of a hemostatic agent such as MPH in patients with externally bleeding wounds, it may be possible to reduce blood loss and prevent the need for blood transfusions. Thus, morbidity and mortality rates may be decreased.

Limitations

It must be noted that the nature of this study precluded the blinding of investigators to the treatment group.

This study was also limited by the fact that no animal model has been universally accepted as optimal for comparison of hemostatic effects produced by wound dressings. It should be emphasized, however, that the model used in the present study was not intended to exactly mimic a clinical situation, but it was meant to serve as a platform for evaluation of the efficacy of dressings used to control high-pressure arterial bleeding. In the present study, the bleeding source was directly visible and accessible, which created a situation unlike any that is likely to occur in the field.

Finally, a scale weight was used for compression in the present study, but manual compression is generally provided in real life situations.

CONCLUSIONS

Application of MPH with the use of a standard level of compression produced by a scale weight that weighed 200 g significantly decreased the time required to achieve hemostasis in a rat model with severe femoral arterial bleeding. MPH may represent an important advancement in the management of topical arterial bleeding that provides significant advantages over other hemostatic agents.

If similar results are achieved in future prospective trials of healthy volunteers, it may be concluded that this agent ensures rapid and successful hemostasis for patients treated in the emergency department, in the field, in the ambulance, and during wartime.

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