Uterine packing with chitosan-covered tamponade to treat postpartum hemorrhage

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Postpartum hemorrhage remains a major cause of maternal mortality and morbidity worldwide with higher rates found in resource-challenged countries. Conventional use of uterotonics such as oxytocin, prostaglandins, and medications to support coagulation, such as fibrinogen and tranexamic acid, are helpful but may not be sufficient to arrest life-threatening postpartum hemorrhage. Severe postpartum hemorrhage leads to an increased need for blood transfusions and the use of invasive techniques, such as intrauterine balloon tamponade, compression sutures, and arterial ligation, as advanced steps in the management cascade. In extreme cases where hemorrhage is resistant to these therapies, a hysterectomy may be necessary to avoid possible maternal death. Uterine packing with a chitosan-covered tamponade is an emerging tool in the armamentarium of the obstetrical team, especially when resources for advance surgical and other invasive options may be limited. Modified chitosan-impregnated gauze was originally described in the management of acute hemorrhage in the field of military medicine, combining the physiological antihemorrhaging effect of modified chitosan with a compression tamponade for the acute treatment of wound bleeding. The first described use in obstetrics was in 2012, showing that the chitosan-covered tamponade is an effective intervention to arrest ongoing therapy-resistant postpartum hemorrhage. Further studies showed a reduction in hysterectomies and blood transfusions. The method is, however, underreported and is not yet an established method used worldwide. To demonstrate the step-by-step application of the intrauterine chitosan-covered tamponade in the management of therapy-resistant postpartum hemorrhage, we have produced a teaching video to illustrate the important steps and techniques to optimize the effectiveness and safety of this novel intervention.

Key words: chitosan, coagulation, intrauterine packing, peripartum hysterectomy, postpartum hemorrhage, tamponade, teaching video, therapy-resistant postpartum hemorrhage, uterine atony, uterine packing

Background

Postpartum hemorrhage (PPH) causes substantial maternal mortality and morbidity and is responsible for a quarter of all maternal deaths worldwide.[1] Conventional use of uterotonics such as oxytocin, prostaglandins, and medications to support coagulation, such as fibrinogen and tranexamic acid, are helpful but may not be sufficient to arrest life-threatening PPH.[2,3]

Blood transfusions, intrauterine balloon tamponade application, invasive techniques, such as compression sutures, and arterial ligation are advanced steps in the management cascade.[4,5] In extreme cases, a hysterectomy may be necessary to avoid maternal death.[6]

Chitosan-covered tamponade and chitin

The chitosan-covered tamponade was originally described in the management of acute hemorrhage in the field of military medicine, combining the physiological antihemorrhaging effect of chitosan with a compression tamponade.[7] Chitosan originates from the shell of sea crustaceans and acts via a physiological pathway related to electrical charges on circulating cells that is independent of coagulation factors. Chitosan is derived from partial deacetylation of chitin and is a natural polycationic linear polysaccharide.[8] The starting element, chitin, is the second most abundant natural polysaccharide after cellulose and is the structural element in the exoskeleton of insects, crustaceans, and the cell walls of fungi.[9] Chitin for chitosan-covered gauze is extracted from *Pandalus borealis*, which is a species of caridean shrimp found in the cold parts of the northern Atlantic Ocean (Figure 1).[10]

Chitosan itself is composed of β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine, which are naturally occurring sugars in the body, randomly distributed within the polymer (Figure 2).[11] Chitosan-covered gauze contains a modified version of chitosan with protonation of the amine group, which gives it the unique mode of action.

The process of reabsorption of chitosan-based products is known to be through enzymatic cleavage by various chitinases (with lysozyme being the most prominent in humans), which leads to a reduction in the molecular weight of the product over time to a level that can either be renally excreted or absorbed. Studies indicate that oligomers having molecular weights of around 5 kDa will be excreted renally. For the body to reabsorb and utilize the chitosan molecule, it is required to be broken down to glucosamine or a glucosamine derivative.[12]

The raw chitosan material has been tested for allergic reactions in humans

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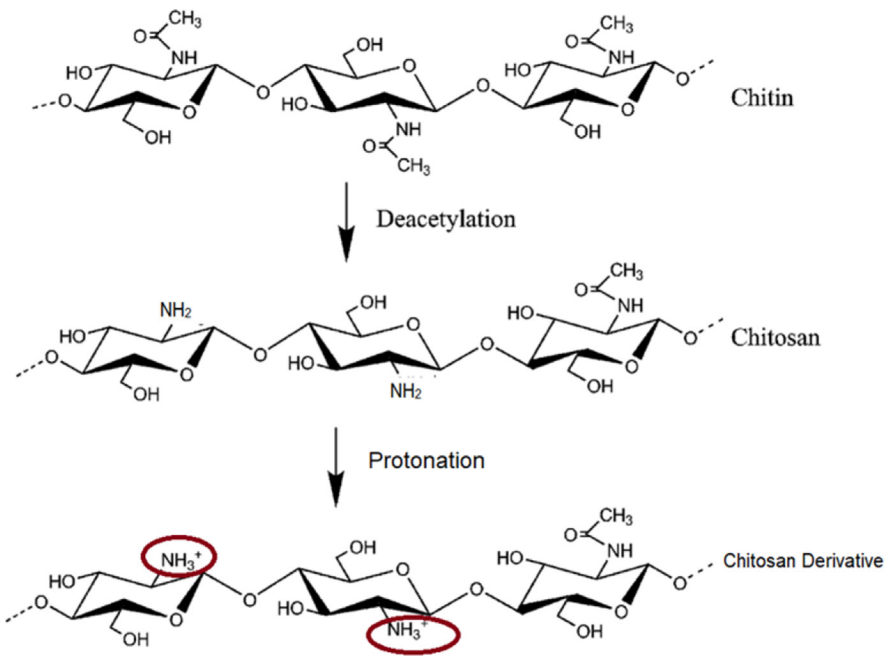
FIGURE 1
The North Atlantic cold-water prawn *Pandalus borealis*

Henrich. Chitosan-covered tamponade to treat postpartum hemorrhage. Am J Obstet Gynecol 2022.

with a known fish or shrimp hypersensitivity, and none of the subjects showed any reaction.[10] Tests on chitosan-covered products have included examination of whether particles may enter the bloodstream, but this was found to not be the case. Histologically examined tissue and other clinical parameters from the treated vessels in a swine model of lethal arterial injury showed some granules on the outside of the treated vessel, as expected, but no particles inside the vessel walls.[13–15]

The chitosan-covered tamponade comprises a base gauze coated on both sides with a proprietary composition that contains modified chitosan in the form of microgranules with a large surface area and granular flakes that are designed for maximum effectiveness. The primary mode of action of the chitosan-covered tamponade is the absorption of water from blood into the granules to form a robust gel pseudoclot. As the water is absorbed, blood components are also amalgamated in the gel to form a coagulum (pseudoclot) at the site of bleeding (which also has adhesive properties to muco-adhere to the surrounding tissue). The formation of the gelatinous mass is also assisted by the cationic nature of the modified chitosan polymer. This positive charge allows it to form electrostatic complexes or multilayer structures with other negatively charged materials, such as red blood cells within the blood, attracting them to the injury site independent of coagulation factors. This is a secondary action to the primary mode of action of creating a gel pseudoclot. The resulting adhesive gel patch acts as a physical barrier to blood loss and consequently works independently of the clotting cascade. The layers of the gel formed between the layers of chitosan-covered gauze further create a barrier to bleeding, enhancing the hemostatic profile. Further stabilization of the wound plug is brought about by the moistened gauze layers adhering together and creating a firm plug.[8]

FIGURE 2
The molecular structure of chitin, chitosan, and the chitosan derivative



Henrich. Chitosan-covered tamponade to treat postpartum hemorrhage. Am J Obstet Gynecol 2022.

Initial use in the military and medical settings

Bennett et al[7] published a review on the clinical use of the chitosan-covered tamponade in the military and medical settings. Based on the emerging evidence at that time in animal studies that showed the efficacy of chitosan in arresting uncontrollable hemorrhage, the United States military incorporated its use in the management of severe bleeding injuries in combat operations.[7,16,17] In 2006, Wedmore et al[18] published the first review on the chitosan gauze in the management of hemorrhage in wounded soldiers. This was a study on 68 cases of military blast and penetrating injury wounds with severe hemorrhage. These included wounds to the chest, groin, buttocks, and abdomen in 25 cases, the extremities in 35 cases, and the neck and facial area in 4 cases. The study showed that in 97% (62/68) of cases, the use of chitosan-covered gauze led to a cessation of bleeding or an improvement in hemostasis. There were no reported complications or adverse events.

Chitosan-covered gauze was shown in a retrospective database analysis of hemostatic agents used on the battlefield to be the only individual hemostatic dressing that was associated with a marked improvement in survival, which was most apparent among the most severely injured.[19] Another study in Afghanistan showed effective hemostasis when chitosan-covered gauze was used as an adjunct to the traditional compression and torniquet methods that are normally

applied in the management of massive traumatic bleeding.[20] There are also reports of successful pelvic packing with chitosan-covered gauze in cases of massive uncontrollable pelvic hemorrhage when conventional surgical attempts to achieve vascular control had failed.[21] After a decade of use and reports in the military field, the Current Tactical Combat Casualty Care guidelines recommended that chitosan-covered gauze should be readily available for use as the hemostatic dressing of choice in the United States military, emergency medical services, and law enforcement agencies.[22]

Other nonmilitary medical specialty reports on the use of the chitosan-covered tamponade in the management of severe hemorrhage have been published. Hatamabadi et al[23] performed a randomized controlled trial in 160 patients with penetrating limb wound injuries among civilians for whom hemostasis was achieved within 5 minutes in 32.5% (26/80) of the control group treated with conventional compression bandages and in 51.3% (41/80) of the intervention group treated with chitosan-covered gauze. There was also significantly less blood loss in the intervention group (P=.001).[23] In the field of cardiothoracic surgery, Millner et al[24] reported on 2 cases with effective application of chitosan-covered gauze to vascular bleeding points in uncontrollable cardiothoracic vascular bleeding following severe injury, achieving hemostasis when other measures such as surgical hemostatic maneuvers, blood and blood product transfusions, cryoprecipitate, factor VII and traditional packing had failed.[24] Similarly, Muzzi et al[25] reported on 2 cases of life-threatening hemorrhage following a cardiotomy when chitosan-covered gauze was used to pack the mediastinum and sternal edges to arrest bleeding that was not responding to conventional treatments. In the field of otolaryngology, head, and neck surgery, Kourelis et al[26] found in a review of 35 patients presenting to the emergency room with uncontrollable, drug-induced severe epistaxis resistant to conventional therapy that packing with chitosan-covered gauze was effective in 91% (32/35) of patients with a mean time to bleeding cessation of 3.5 minutes.[26]

Chitosan-covered tamponade in obstetrics

In obstetrics, the chitosan-covered tamponade was first described in 2012 by Schmid et al[27] as an effective intervention to arrest ongoing, therapy-resistant PPH. In this case, a 32-year-old woman developed a massive PPH owing to uterine atony following an elective cesarean delivery for placenta previa, which was resistant to uterotonic medications including sulprostone infusion. A relaparotomy was performed because of persistent bleeding. B-Lynch uterine compression sutures were unsuccessful, and despite an intracavity curettage and in the face of ongoing bleeding requiring a massive blood transfusion of 10 units of blood and other blood products, the decision was made to tamponade the uterine cavity with a chitosan-covered tamponade transvaginally. Hemostasis was achieved and a hysterectomy was avoided.

A further study on 19 patients highlighted the potential use of chitosan-covered gauze to treat severe PPH secondary to uterine atony, placenta accrete or increta, and coagulopathy states for which a hysterectomy seemed inevitable. In all but 1 case the bleeding stopped and further interventions were avoided. Results demonstrated that chitosan-covered gauze was a viable option in the treatment of severe PPH, and data showed that the rate of peripartum hysterectomies was reduced by 75% (8 vs 2; odds ratio, 4.27; P=.044) in the 18 months after introduction of chitosan-covered gauze compared with the 18 months before introduction.[28]

A further report of case studies showed the effectiveness of chitosan-covered gauze in stopping bleeding over a range of different forms of serious obstetrical bleeding.[29] In a recent retrospective study of 78 patients with PPH, 47 (60.3%) received a chitosan-covered tamponade and 31 (39.7%) received a balloon tamponade at the Charité University Hospital in Berlin with more than 5000 deliveries per year; there was no considerable difference in the postpartum vital signs, blood loss, hemoglobin levels, admission to the intensive care unit, and inflammatory markers between the groups. However, it was noted that there was a reduction of 50% in the incidence of peripartum hysterectomy in the 18 months after the introduction of the chitosan-covered gauze when compared with the 18 months preceding it. The chitosan-covered tamponade was described as being less complicated to apply with less pain and tamponade dislocation and the ability to tamponade the vagina simultaneously.[30] We have also reported on the use of the chitosan-covered tamponade in combination with intrauterine balloon therapy.[31] A further published review of our experience by Biele et al[32] in 2022 also showed a 78% reduction in the postpartum hysterectomy rate from 9 to 2 cases in the 31 months after introduction of chitosan-covered gauze when compared with the 31 months before introduction.[32]

The chitosan-covered tamponade seems to be an emerging tool in the armamentarium of the obstetrical team and can be used as an adjunct in the management of PPH, especially in areas where resources for advance surgical techniques and other invasive options may be limited. It may be specifically advantageous because it acts independently of the coagulation cascade and it may be particularly beneficial in PPH cases with already deranged coagulation.

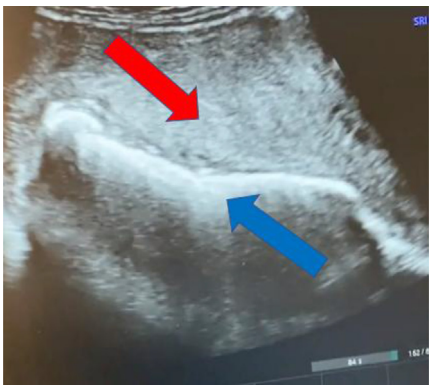
To date, there have been no reported adverse risks associated with the chitosan-covered tamponade. Removal after 18 to 24 hours and antibiotic prophylaxis is recommended during this time. The risk of ineffective intrauterine packing and isolated cases of incomplete removal have been reported.[28]

To perform a prospective, multicenter, randomized placebo-controlled trial for an emergency intervention that may at times be a last resort in the face of life-threatening hemorrhage can be challenging. Nevertheless, such a trial would be useful to demonstrate the effectiveness and safety of the use of a chitosan-covered tamponade compared with other therapeutic interventions such as the balloon tamponade. Ethical approval for such a study is currently being

formulated and in progress. However, when confronted with life-threatening hemorrhage, the benefits of the chitosan-covered tamponade seem, from our point of view, to be an excellent and easy to apply method.

To describe the application of the intrauterine chitosan-covered tamponade in the management of therapy-resistant PPH, we have produced a teaching video to demonstrate the important steps and techniques required to optimize the effectiveness and safety of this novel intervention (Video). In a simulated scenario, we show the application technique supported by ultrasound with the patient in lithotomy position. When possible, but not as a prerequisite, the use of ultrasound can be incorporated to confirm the absence of retained products before the application of the tamponade, and we also demonstrate during the time of intrauterine packing the sonographic surveillance of the uterus to optimize the tamponade packing by visualizing the uterine cavity (Figure 3).

FIGURE 3
Ultrasound image illustrating uterine packing with a chitosan-covered tamponade



To illustrate the uterine packing, here is an ultrasound image (*inset*) with a transabdominal longitudinal view of the uterus (*red arrow*) showing the uterine cavity packed with the chitosan-covered tamponade transvaginally (*blue arrow*). Ultrasonographic evaluation is, however, not necessary to pack the uterus with a chitosan-covered tamponade.

Henrich. Chitosan-covered tamponade to treat postpartum hemorrhage. Am J Obstet Gynecol 2022.

On removal, inspection of the end of the fabric for an intact edge to determine integrity and completeness is recommended. In addition, we demonstrate the application of a suture to the leading end of the intrauterine tamponade, which, when visualized on removal 18 to 24 hours later, confirms complete removal. As an extra-safety maneuver, we highlight the presence of the tamponade in these patients with an armband that is only to be removed when the intrauterine packing is simultaneously removed. In the nonhospital setting and without technical and instrumental support, it is also possible to pack the uterus with the chitosan-covered tamponade manually.

Recommendations

We recommend that every birth attendant in the hospital and in the outpatient setting consider having the chitosan-covered tamponade readily available and prepared for use, similar to its use in the fields of battle. Given that it has been shown to be fast-acting, clinically effective, safe, and easy to use with the potential to avoid high-cost interventions such as a peripartum hysterectomy, the chitosan-covered tamponade can be incorporated as a second line intervention or adjunct in the management protocol for PPH. ■

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