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Basic Experiments to Develop Temporary Packing Material Using a Polymer Gel to Control Solid Organ Hemorrhage

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Abstract

Background: Towel or gauze packing is usually applied as a temporary hemostatic method in damage control surgery, but "repacking" is sometimes required at the planned reoperation because of re-bleeding after removal of these materials when they adhere strongly to the injured surface. This experiment was conducted to determine the possibility of reliable packing and safe removal using a supramolecular gel as a new packing material. The supramolecular material, which consists of β-cyclodextrin (CD), adamantane (Ad) andpoly acrylamide (pAAm) (β-CD-Ad pAAm gel), has highly flexible, tough, and self-healing characteristics.

Materials and Methods: Irregular shaped (3 cm to 4 cm in diameter) gel lumps were prepared from a β-CD-Ad pAAm gel sheet. These gel lumps were used to fill a blunt disruption prepared on the right lobe of porcine liver, and towel packing was carried out by covering the gel lumps to ensure they adequately adhered to the damaged liver surface. After 30 mins the towel and gel lumps were removed, and the area was examined macroscopically for appropriate adhesion to the injured surface, hemostatic efficacy, removability of the gel lump, and presence or absence of re-bleeding.

Results: The β-CD-Ad pAAm gel fragments tightly adhered to each other and were re-shaped to fit to the uneven lacerated liver surface, although self-adhesiveness declined when blood was attached to the gel, leading to a reduction in stretchability. However, it was possible to attach free-shaped gel lumps to the complex damaged liver surface. Compression of the lumps from above with a towel enabled packing as usual. When the packed gel lump was removed, adhesion to the injured surface was not observed, and it was possible to remove the gel without causing re-bleeding.

Conclusion: This basic experiment suggests that the polymer gel consisting of β-CD-Ad pAAm may be used as packing material instead of conventional gauze or towel packing and that it does not cause re-bleeding on removal. In the near future, trauma surgeons might be able to use a revolutionary hemostatic material for abdominal organ injury.

Keywords: Damage control surgery; Hemostasis; Cyclodextrin; Supramolecule

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Background

In a hemorrhagic shock patient suffering from severe trauma, platelets and coagulation factors are consumed due to massive bleeding, and because the body surface and cavity are exposed in the field, the injured patient's core temperature drops markedly in the emergency department or in the operating room. Hypothermia and blood dilution by a large amount of infusion solution inhibits the coagulation system. In addition, insufficient tissue flow accompanied by hemorrhagic shock leads to metabolic acidosis, which causes a vicious circle that promotes coagulopathy and leads to further bleeding [1]. Even by continuing the hemostatic operation forcibly until the blood transfusion runs out at this point, hemostasis cannot be achieved under failing coagulation function, resulting in a poor prognosis. To cut off this vicious circle, surgery should be terminated temporarily with only the necessary minimum treatment for bleeding and contamination followed by correcting for hypothermia, replacing the coagulation factors, and improving the hemodynamics.

Damaged Control Surgery (DCS) is a treatment strategy to achieve this policy [2-5]. The surgeon terminates the operation after controlling hemorrhage or closing the ruptured intestine, and carries out a planned reoperation after improving the patient's general condition by intensive care. The

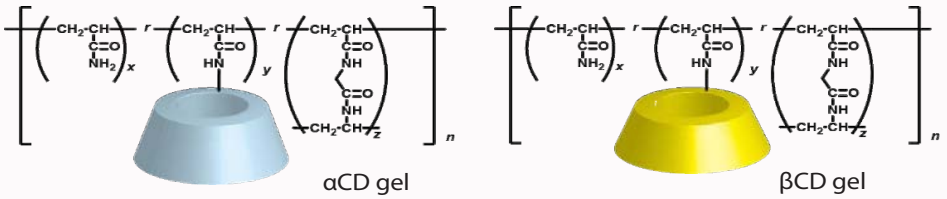


Figure 1: Basic chemical structureof cyclic oligosaccharide (CD).

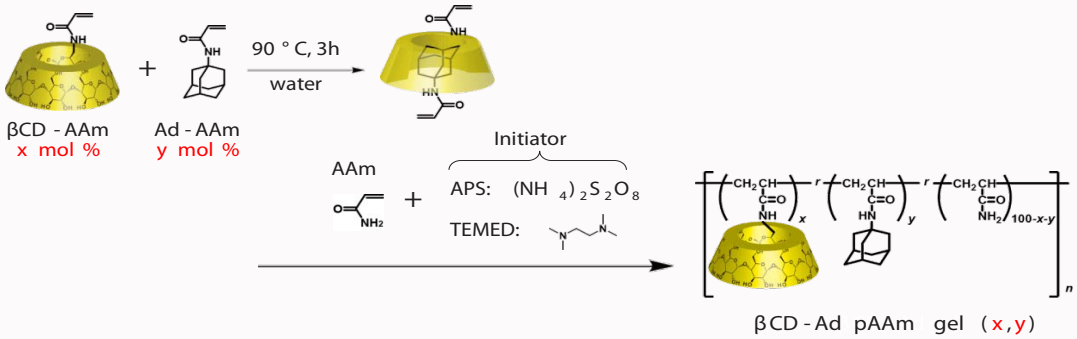


Figure 2: Structure and creation of β-CD, adamantane (Ad) andpoly acrylamide (pAAm) (β-CD-Ad pAAm gel).

most commonly used and classic measure in DCS is temporary packing using gauze or towels for diffuse bleeding from the damaged surface of organs such as liver or the retroperitoneum [6,7]. However, since these materials strongly adhere to the injured site, there is a high risk of re-bleeding upon careless removal of the packing, and trauma surgeons often experience this problem. One of the key factors for the success of DCS is the certainty of packing and safety upon its removal.

Cyclodextrin (CD) is a cyclic oligosaccharide in which several molecules of D-glucose are linked by α-1,4 glycoside bonds and have a cyclic structure. Cyclic oligosaccharide is classified as α-CD (hexamer), β-CD (heptamer), γ-CD (octamer) according to the number of glucopyranose units contained in one molecule of CD. CD has a stable structure against acid-bases, amylase, heat, and it is widely used as a synthetic material consisting of supramolecules with cyclic structural properties (Figure 1). The Harada Group in Osaka University has developed supramolecular polymeric materials with various properties, such as macroscopic self-assembly, self-healing, and shape memory, using the host-guest bond between host CD and hydrophobic guest [8-15]. For example, Yamaguchi and colleagues found a phenomenon in which the separated α-CD-gels (host) and azobenzene-gels (guest) were assembled in visible light (wavelength at 430 nm) and dissociated by ultraviolet at 365 nm [14]. Nakahata reported that a host-guest bond has the switch function of a sol-gel and a self-repair function of cutting and adhesion by oxidation-reduction with NaClO aq. and glutathione [13]. The Harada Group found that a supramolecular material consisting of β-CD, adamantane (Ad) and poly acrylamide (pAAm) (β-CD-Ad pAAm gel) has highly flexible, tough, and self-healing features [15] (Figure 2).

Accordingly, the authors investigated whether these properties of supramolecules, especially of the β-CD-Ad pAAm gel, can be utilized as a new packing material for bleeding sites that are difficult to control in DCS.

Methods

This fundamental experiment was approved and conducted in accordance with the Declaration of Helsinki and the Regulations of Animal Experimentation of the Committee on Animal Experiments of Nippon Medical School (No. 27-001).

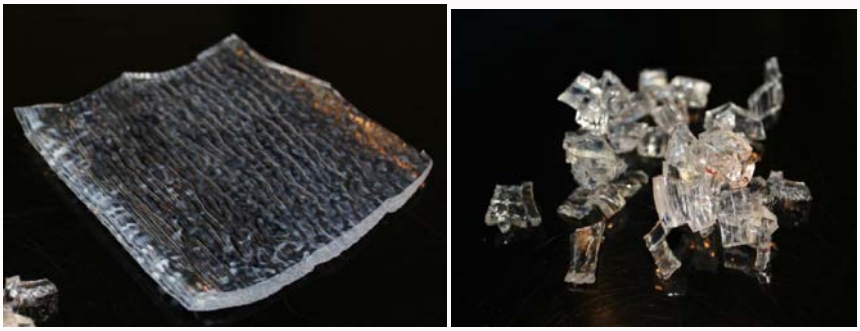
A Large Yorkshire pig (female) weighing 44.5 kg with 24-hr fasting was administered 4.0 ml of pentobarbital followed by intubated and placed under general anesthesia (1% to 2% isoflurane). Anaesthesia was maintained with 2% isoflurane and muscle relaxant. Vital signs were monitored intraoperatively by a pulse oximeter and electrocardiograph, and hemodynamics was maintained by administering Ringer solution. A celiotomy was carried out *via* amidline abdominal incision and a blunt disrupted liver injury of 3-cm maximum depth and 10-cm maximum length on a right lobe of the liver was prepared with Péan forceps. Several ligations were performed to stop active bleeding, but venous bleeding from other injured surfaces was left untreated.

Next, the β-CD-Ad pAAm gel sheet provided by the Harada Group (Figure 3A) was cut with scissors to form fragments with a length of about 5 mm to 7 mm (Figure 3B), and these were assembled randomly to prepare many irregular shaped small (3 cm to 4 cm in diameter) gel lumps. To ascertain whether these gel lumps could serve as packing material for hemorrhage control, they were arranged to fill the damaged site of the liver and towel packing was carried out by covering them to enable adequate adherence to the damaged liver surface.

After 30 mins, the towel and gel lumps were removed, and the area was observed macroscopically for appropriate adhesion to the injured surface, hemostatic efficacy, removability of the gel lump, and presence or absence of re-bleeding.

Results

Since the β-CD-Ad pAAm gel is highly stretchable and strongly self-adhesive, it was easy to assemble small fragments of β-CD-Ad pAAm gel. The β-CD-Ad pAAm gel fragments tightly adhered to each other and the lump was shaped to fit to the uneven lacerated liver surface (Figure 4), although self-adhesiveness declined when blood was attached to the gel.



(A) (B)

Figure 3: A 10 cm × 10 cm β-CD-Ad pAAm gel sheet (A) was fragmented to pieces 5 mm to 7 mm in length (B).

Figure 4: The β-CD-Ad pAAm gel fragments were assembled randomly to form small (3 cm to 4 cm of diameter) gel lumps due to the properties of high stretchability and close contact with each other.

However, it was possible to attach free shaped gel lumps to the complex damaged liver surface (Figure 5A). The gels were compressed from above with a towel to conduct packing in the usual manner (Figure 5B). When the packed gel lump was removed, adhesion with the injured surface was not observed, and it was possible to remove the gel without causing re-bleeding.

Discussion

Packing in DCS is a surgical procedure to treat uncontrollable bleeding from an injured organ or tissue when the coagulation function declines or fails [16]. Packing is frequently used for parenchymal organ injury, such as hepatic laceration. The success or failure of packing depends on the adherence to the damaged surface of the packing material used and the compressive force at the time of packing. Strong anchoring and compressive forces produce a strong hemostatic force and enable successful hemostasis. On the other hand, when depacking during a planned reoperation, a careful procedure that does not stimulate the packed injured site is required, and the surgeon sometimes experiences re-bleeding and has to perform repacking.

Many hemostatic materials, including both flowable and non-flowable types, have been developed to cope with various surgical issues as well as simple packing by gauze or towels [17-23]. Both of these have advantages and disadvantages, and definitive hemostatic materials or hemostatic agents have not yet been established. For example, a well-known non-flowable hemostatic tool is Combat gauze™ [24]. This is gauze permeated with kaolin, which was commercialized in 2007. In war surgery in Iraq and Afghanistan, and in subsequent studies, it has been reported that Combat gauze™ is effective for hemostasis against arterial bleeding, particularly in injuries of the extremities. Sena and colleagues examined the potential of combat gauze as a packing material for liver injury using a porcine model and claimed that it reduced the amount of bleeding compared to conventional materials [25]. Inaba et al. also reported that Celex and Combat gauze™ were effective for damage control packing in a porcine liver injury model. On the other hand, there are many complications of small intestinal obstruction caused by adhesion [26].

Traditionally, gauze and/or towels are used as packing materials, but in recent years a popular method is to wrap them by surgical drapes. However, this method can create a gap between the damaged surface, which has complex irregularities, and the wrapped packing materials, allowing blood to permeate into the gap, which may reduce the packing effect. The ideal packing material is "a material that closely adheres to the complex damaged surface and can be removed cleanly from the tissue". One of the key factors for the success of DCS is the certainty of packing and safety at the time of removal and we have focused on the ideal packing material that satisfies these requirements.

The Harada Group in the Project Research Center for Fundamental Sciences, Graduate School of Science at Osaka University is conducting research on the structural control of supramolecular complexes using cyclodextrin. Cyclodextrin (host molecule) has the clathrate ability to incorporate guest molecules into its inner cavity. The Harada Group discovered that this host-guest polymer has high flexibility, toughness and self-healing when using adamantane as a guest molecule [15]. If this gel material can be used for packing in DCS, it may be possible to bring the gel into close contact with the uneven surface of organ injuries by using the feature of the supramolecular complex and to easily withdraw it from the tissue upon removal. Accordingly, in this study, we aimed to conduct a basic experiment on the effect on hemostasis of this supramolecular gel when used as a packing material, or what effect it has on injured organs. If β-CD-Ad gel achieves the same hemostatic effect as that obtained with conventional materials such as gauze and towels, and resolves the re-bleeding problem on packing removal, it will be a promising technique for clinical application in the future and provide trauma surgeons with a breakthrough hemostat strategy for exsanguinating trauma.

Experimental results revealed that the β-CD-Ad pAAm gel

was effective in attaching to the injured uneven surface and that re-bleeding at the time of packing removal could be avoided. The results of this experiment demonstrated that the gel used was suitable for close contact with a damaged irregular surface because it has the properties of free assembly after fragmentation and strong re-adherance. Furthermore, the results showed that this gel could reduce the risk of re-bleeding during depacking because no adhesion to the tissue occurred. These two points satisfy the conditions required for a packing material for DCS.

On the other hand, it was found that when the blood entered between the sticking gels, adhesion was inhibited. It is still unknown how much the gel's characteristics are affected by the presence of blood. In addition, it has been confirmed that β-CD, Ad, and pAAm constituting β-CD-Ad pAAm gel have no influence on the human body, but the influence (toxicity) when these are made into a copolymer remains unconfirmed. Clinical packing is usually carried out during a period of 24 hr to 48 hrs in almost all cases, which should not present a major problem because the packing materials are removed in the planned reoperation and never remain permanently in the body. However, the influence of β-CD-Ad pAAm gel on the human body is an important issue in clinical applications even for a short time of use.

The limitations of this research were as follows; the experimental animal with an injured liver had no bleeding tendency because it was healthy and hemodynamically stable. This was an experimental environment that did not match the actual human clinical setting. Judgment of the hemostatic efficacy and adhesion to the injured surface was limited to macroscopic evaluation, so that a quantitative evaluation of the required conditions for a packing material was not made. For example, a comparison of results obtained with traditional gauze and towels was not performed. Another key limitation was the use of an animal with a coagulation and fibrinolytic system that differs from humans.

This experiment was fundamental for exploring the use of a CD-host-guest gel as a packing material, but a quantitative evaluation and comparison with other materials should be further investigated. As the CD-host-guest gel is considered to have no adverse effect on the human body due to its composition, hurdles for clinical application to humans may be few assuming adequate ethical considerations.

Conclusion

The findings of this basic experiment suggest that the polymer gel, β-CD-Ad pAAm, can be used as packing material instead of conventional gauze or towel packing and that it does not cause re-bleeding on removal. It is necessary to study the shape of the gel that adheres securely to the larger damaged surface, microscopically observe the area between the gel and damaged organ surface, and combine the gel with other hemostatic agents using an experimental model with hemorrhagic shock and bleeding tendency. In the near future, trauma surgeons might be able to use a revolutionary hemostatic material for abdominal organ injury.

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