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Author's response to Reviewer A

First of all, we greatly appreciate your favorable review of our manuscript. In addition, we would also like to thank you for your valuable comments and suggestions. In response to the points that you raised, we offer the following answers.

Minor revisions

1) **In case of telling the safety of topical hemostatic agents, comprehensive evaluation of this products will be needed. Therefore, not only nine postoperative adverse effects you described in this manuscript but also general adverse effect such as liver dysfunction, renal dysfunction, prolonged febrile, wound infection should be indicated.**

➔ Thank you for valuable and precise comments. As per your suggestion, we agree that adverse general dysfunctions, such as liver/renal/postoperative fever/wound infection, should be mentioned for reader comprehension. In the present study, there were no critical general dysfunctions except for one case of respiratory distress. Following your comments, we have added additional information to the Results section, as follows:

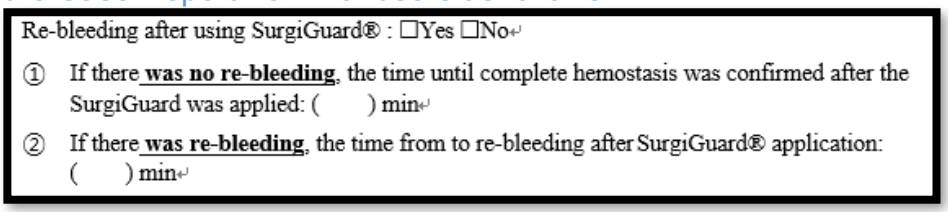
➔ Page 8)

Adverse effect

A total of nine postoperative adverse effects were reported: bleeding, postoperative intestinal obstruction, abscess, fever, leg swelling, and respiratory dysfunction. There were no general dysfunctions such as liver/renal dysfunction, postoperative fever or localized wound infection. The most common adverse effect was bleeding or leakage from the treated site (3 patients, 33.3%), and one patient required an intraoperative transfusion. Postoperative intestinal obstruction occurred in 2 patients (22.2%). However, these complications did not directly correlate with SurgiGuard® use (**Table 4**).

2) **I know how difficult the efficacy for local hemostasis during surgery, but please describe the method to measure "the mean time to hemostasis". Completely improvement of oozing type of bleeding or recovery from pulsatile bleeding to oozing type of bleeding.**

➔ As you have also pointed out, it is difficult to estimate the exact efficacy of local hemostasis during surgery. However, we prepared a certain inquiry in the Case Report Form for users as follows:


Re-bleeding after using SurgiGuard® : ☐Yes ☐No

① If there **was no re-bleeding**, the time until complete hemostasis was confirmed after the SurgiGuard was applied: ( ) min

② If there **was re-bleeding**, the time from to re-bleeding after SurgiGuard® application: ( ) min

"Complete hemostasis" was defined as any type of woozing or pulsatile bleeding that was not observed at the bleeding site after application of SurguGuard®. We described the specific definition of "the mean time to hemostasis" in the manuscript.

➔ Page 5)

Study population and study design

We collected the clinical data of patients who underwent surgery at seven different tertiary medical centers between January 2018 and December 2018. A total of 22 surgeons form 12 different departments participated in this study. To eliminate bias, all types of surgeries using a full anticoagulation agent or medication during surgery, such as cardiopulmonary surgery, were excluded from the study. Patients who underwent minor vascular surgery and kidney/liver transplantation with limited-dose heparin were included. We retrospectively investigated sex, diagnosis, surgical department, co-morbidities, medications, and perioperative findings (surgery, estimated blood loss, transfusion, serum hemoglobin level, time to hemostasis, drain usage). "Hemostasis" was defined as any type of woozing or pulsatile bleeding that was not observed at the bleeding site after application of SurgiGuard®. In cases of rebleeding even after application of SurgiGuard®, the time until rebleeding occurred was also recorded. As the total patient cohort was heterogeneous, we divided it into two groups to assess the SurgiGuard® product: group A, who used SurgiGuard® alone (n=248), and group B, who used SurgiGuard® with other hemostatic products (n=559). All surgery types were categorized as major (total operative time ≥ 4 hours) or minor surgery (total operative time < 4 hours; **Figure 1**).

3) As you know, full-dose heparin is required in cardiac surgery with cardiopulmonary bypass, and the situation of hemostasis after CPB is quite

different, so these cases should be excluded.

➔ As per your comments, in cardiac surgery such as cardiopulmonary bypass, full-dose heparin is required during the operation. In this study, 40 patients (5% of the entire cohort) underwent surgery in the thoracic or cardiovascular departments. All cases of the thoracic and cardiovascular department that enrolled in this study were all lung surgeries, such as lobectomy or bilobectomy, segmentectomy, or wedge resection for lung cancer. Similar to the operations in other departments included in this study, surgeries containing potential bias that could have significantly interfered with this analysis (e.g., cardiopulmonary bypass) were thoroughly excluded, except for minor vascular surgery or kidney/liver transplantation surgery using limited-dose heparin. To clarify the purpose and results of this study, we have added detailed comments regarding the surgical exclusion criteria.

➔ Page 5)

Study population and study design

We collected the clinical data of patients who underwent surgery at seven different tertiary medical centers between January 2018 and December 2018. A total of 22 surgeons form 12 different departments participated in this study. To eliminate bias, all types of surgeries using a full anticoagulation agent or medication during surgery, such as cardiopulmonary surgery, were excluded from the study. Patients who underwent minor vascular surgery and kidney/liver transplantation with limited-dose heparin were included. We retrospectively investigated sex, diagnosis, surgical department, co-morbidities, medications, and perioperative findings (surgery, estimated blood loss, transfusion, serum hemoglobin level, time to hemostasis, drain usage). "Hemostasis" was defined as any type of woozing or pulsatile bleeding that was not observed at the bleeding site after application of SurgiGuard®. In cases of rebleeding even after application of SurgiGuard®, the time until rebleeding occurred was also recorded. As the total patient cohort was heterogeneous, we divided it into two groups to assess the SurgiGuard® product: group A, who used SurgiGuard® alone (n=248), and group B, who used SurgiGuard® with other hemostatic products (n=559). All surgery types were categorized as major (total operative time ≥ 4 hours) or minor surgery (total operative time < 4 hours; **Figure 1**).

4) The type or font of reference is different, please modify the same font in all manuscript.

➔ Thank you for your valuable comments. As per your suggestion, we have modified the entire manuscript using the same font, including the References section.

➔

➔ Page 11)

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Author's response to Reviewer B

Oxidized regenerated cellulose is effective for hemostasis in various surgeries. however on the other hand, oxidized regenerated cellulose is also concerned on absorbable adhesion barrier in recent years. the discrepancy between hemostasis and adhesion barrier should be argued in the discussion. This article is an excellent outcome. But the authors should explain the mechanism of oxidized regenerated cellulose.

➔ We appreciate your valuable comments. We agree with you that there was a discrepancy between use as the hemostatic agent and the anti-adhesion agent in ORC. In the past several decades, ORC has mainly been used as a hemostatic agent for bleeding control in various surgeries. However, its adhesion barrier effects of ORC and ORC-derived products have been reported. Numerous approaches using solid or liquid barriers have been developed to reduce adhesion. Biogradable solid barrier materials with hyaluronic acid-carboxymethyl cellulose films (Seprafilm, Genzyme) and polymer solution barriers, such as carboxymethyl cellulose and sodium hyaluronic acid, have been reported as postoperative anti-adhesion materials. Although several studies have reported that ORC and its derived products help prevent adhesions, some studies have indicated that comorbidity increases due to abscess formation in relation to abdominal surgery, especially in the case of liver surgery. Recently, a spray-type ORC-related anti-adhesion product was introduced; however, there is still a debate regarding abscess formation and complications. However, according to a large cohort meta-analysis, there is evidence that ORC clearly reduces the adhesion incidence rate, although this is not statistically significant compared to other hyaluronate carboxymethylcelluloses and icodextrin. (Ten Broek, R.P.G et al. "Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis." Lancet 383(9911): 48-59.) Following your advice, we have added these facts to the Discussion section.

➔ Page 9)

A recently developed and advanced form of ORC can aid in hemostasis through calcium and sodium ion interactions, acid-induced small vessel contraction, and sealant properties. In addition, ORC acts as a support matrix for the initiation and

formation of the clot. These material-derived products can be molded into different shapes and sizes, and are compressible without loss of hemostatic ability (24). ORC has great potential with minimum cost, low rate of thrombotic complications, and low disease transmission risk. Moreover, it provides the benefit of a long shelf-life (11). ORC has also been applied for dressings, which are versatile and do not require wounds to be of a certain duration before application (25). Furthermore, the ORC not only shows an excellent hemostatic effect but has also emerged as an effective adhesion barrier over the past several years. In various abdominal surgeries, ORC and its derived products have proven to be effective and feasible for preventing postoperative adhesion events (26-28). According to a large cohort meta-analysis, ORC significantly reduced the incidence of adhesions, and no trials have reported data on reoperation for adhesive small bowel obstruction (29). When the sheet form of the ORC is placed to cover the surgical site, it changes into a gel form within 24 days, and the ORC is degraded by phagocytosis by macrophages. During tissue repair, fibroblasts, epithelial cells, and endothelial cells are stimulated to increase tissue-reinforcing efficacy, which is thought to act as an adhesion barrier (17,30).

Author's response to Reviewer C

I understand your attempt to show benefit and usability of your product, but this study basically was an ease of use and not efficacy. There are no hard endpoints, no time to hemostasis for each product and mixing multiple agents, although may be a common practice, to show efficacy of your product is not possible.
I also feel more background is needed on your product when you describe it: you said low pH (what is it?), is dissolves (what is the dissolution time invitro and invivo?) indicated use- (the bleeds in the study are not well characterized etc)
So I feel that as a physician, what information am I getting from this study that would clearly characterize the product, it's utility and safety above current standards of care?

➔ We fully understand your concerns about the absence of strong endpoints. This study was based on an extremely heterogeneous cohort who had undergone various surgeries, various divisions, and different surgeons. We are aware that it is difficult to demonstrate the efficacy of each practice and

combination when mixing a specific hemostatic time and multiple agents for each product. However, we believe that this demonstrates the “generality and versatility” of the product. The results of this study were obtained by analyzing more than 800 patients who underwent surgery. The results of our study indicate that this hemostatic product can be used for a extremely wide range of times, situations, and surgeries.

Basically, SurgiGuard is same kind of product, Surgicel. In in vitro studies, this product was suspended in water and no appreciable solvation occurred; however, a drop in pH lower than 2.5 was observed. Unlike oxidized regenerated cellulose, neutralized oxidized regenerated cellulose (NORC) behaves as a polyanion if mild bases such as sodium carbonate and pyridine are added. (Dimitrijevich, S. D., et al. (1990). "Biodegradation of oxidized regenerated cellulose." Carbohydr Res 195(2): 247-256.) When neutrality is maintained, ORC begins to curl and transforms into a gel form. In in vivo studies (including previous papers reported by our group), after 24 h post-implantation, the product becomes completely gelatinous, and within 48 h, only small fragments remain. It also indicated a rapid decrease in the pH (~2.5) of the fluid surrounding the site of implantation of the ORC. We believe that this mechanism enhances antibacterial effects. (Kim, S. H., et al. (2016). "Efficacy of the SurgiGuard in partially hepatectomized pigs." Korean journal of hepato-biliary-pancreatic surgery 20(3): 102-109.) (Kim, S. H., et al. (2017). "Efficacy of Oxidized Regenerated Cellulose, SurgiGuard®, in Porcine Surgery." Yonsei medical journal 58(1): 195-205.)

The indication for use of SurgiGuard is stated as follows: “During operation, it assists the hemostasis for capillary and venous, small artery bleeding.” It cannot however be used as contraindication for “packing or wadding,” “skeletal damage,” and “large artery bleeding.” We believe that the surgeons who participated in this study adhered faithfully to the suggested indications. A situation not precisely quantified but generally corresponding to the Lewis bleeding scale of grades 1 to 2 was considered. In cases of grade 3 or 4 disease, physical bleeding control, such as suturing or ligation, was performed not only using a hemostatic agent.

Following your comments and advises, we amended manuscript as follows.

➔ Page 4-5) Introduction

SurgiGuard® (Samyang Biopharmaceuticals Corp., Seoul, Korea) is an absorbent hemostatic agent based on ORC. It is a hemostatic supplement used when other methods, such as the ligation of capillaries, veins, and arterial bleeding, are ineffective during surgery (16). The carboxyl group of oxidized cellulose has a low pH (acidity) through an oxidation reaction to promote hemostatic action and inhibit bacterial growth. In the case of in vitro, the product is suspended in water, and no appreciable solvation occurs; however, a drop in pH lower than 2.5 is observed. In in vivo studies (including previous papers reported by our group), after 24 h post-

implantation, it has been noted that the product becomes completely gelatinous, and within 48 h, only small fragments remain. A rapid decrease in the pH (~2.5) of the fluid surrounding the site of implantation of the ORC has also been observed. (17). The effectiveness of SurgiGuard® has been demonstrated to be equivalent to existing hemostatic agents in several animal studies, and the safety of the product has been demonstrated through biocompatibility tests and antimicrobial tests by NAMSA (Medical Research Organization®, Toledo, OH) (18).

➔ Page 6)

SurgiGuard®

SurgiGuard® is a type of ORC capable of assisting in managing small vessel bleeding. It is designed to achieve hemostasis when conventional surgical techniques are not available or are impractical. Indication for use is as follows: "During the operation, this product assists the hemostasis for capillary and venous, small artery bleeding" Thus, this product generally applied in a situation corresponding to the VIBe scale grade 1 or 2. Four types of SurgiGuard® products were used in this study (**Figure 2**). SurgiGuard Original® is the most common and has long and widely been used in a variety of surgeries. It offers good visibility of the surgical site due to the sheer knit structure. SurgiGuard Fabric® is denser than SurgiGuard Original® and made for heavier bleeding with faster hemostasis. In contrast, SurgiGuard Fibrillar® can be shaped or molded to various shapes for optimal adherence or used in multiple sites. Finally, SurgiGuard Non-woven® is an advanced product for maximized effect and superior handling. The non-woven structure increases surface contact wih the bleeding site and can be applied not only in open surgery, but also minimally invasive surgery.

I feel there are many weakness to the paper.
1. this is a retrospective analysis with no validated method to assess degree of bleeding
2. Multiple products were used and although non-woven formulation had the most use, there is no consistency of how they were used in a multitude of other modalities, ie with/without thrombin, etc.
3. The scale they used was subjective as to how surgeon perceived the utility of the product without any hard endpoints even as a retrospective analysis
I just don't feel this paper adds to body of evidence in the ORC area. There

should be a head to head study done with SurgiGuard and like products with a validated bleeding scale and hard endpoints.

➔ As the reviewer pointed out, this was a retrospective study that did not accurately assess the degree of bleeding. However, through a medical record review, we attempted to show the degree of bleeding by presenting indirect evidence of the amount of bleeding via the drain and the degree to which Hb dropped accordingly. In addition, because various surgeries, divisions, and surgeons were freely included, the products used with the SurgiGuard seemed to be inconsistent. However, except for one special case in Group B, thrombin agents were not used because the effect was halved by SurgiGuard's low pH.
However, as the reviewer stated, the present study was very subjective to the surgeon, and we agree that the hard endpoint was unclear. Further head-to-head and randomized controlled studies to confirm the effectiveness and safety of SurgiGuard are planned and in process. We have added these limitations in the revised manuscript.

➔ Page 10)
Despite encouraging results, this study has certain limitations. First, this study was based on a survey that received responses from a surgeon who performed various surgeries. Thus, one of the main challenges of this study is that the results reflect subjective points of view and experiences. the degree of bleeding Second, due to the heterogenousity of the analyzed study group, we did not sufficiently investigate the unique characteristics of each surgey. With same contexts, the degree of bleeding was not accurately assessed using confirmed bleeding scale as VIBe SCALE (The Validated intraoperative bleeding scale) (35). Third, this study was focused on a short-term outcome survey, and it was not possible to investigate long-term complications, such as abscess or mass-like foreign body, the most common complication of ORC-derived hemostatic agents. As various surgeries and divisions were included, the endpoint of this study was unclear. Further studies, such as head-to-head, randomized controlled cohorts, are required to investigate not only short-term but also long-term complications, taking into account the characteristics of each surgery. Moreover, research on which type of SurgiGuard® is useful and effective under what circumstances should be accompanied.

Further comments please see pdf attached.

➔ Following your comments, we amended the attached PDF file. In addition,

we have added the following recommendations:

➔ Page 3)

Background: SurgiGuard® is an absorbent hemostatic agent based on oxidized regenerated cellulose. The efficacy, effects and safety of SurgiGuard® are equivalent to existing hemostatic agents in animal experiments. This study was designed to confirm that the use of SurgiGuard® alone is effective, safe and feasible compared to combination with other hemostatic methods.

➔ Page 5)

To confirm that sustained use of this hemostatic material is feasible, it is important to clinically determine that the use of SurgiGuard® is effective compared to combination use with other hemostatic methods. Therefore, this study retrospectively reviewed data collected from patients who used SurgiGuard® to assess its effectiveness , safety and feasibility.

➔ Page 4)

Perioperative bleeding is a major concern for surgeons, and efforts have been made by numerous surgeons and researchers to prevent perioperative bleeding (1). The reported prevalence of postoperative bleeding is 0.9-10% in various major surgeries, such as hepatectomy (2), pancreatic surgery (3), gastrointestinal tract surgery (4,5), cardiovascular surgery (6,7), nephrectomy (8), and liver transplantation (9). On a closer look, various recent studies have reported that the prevalence of capillary, venous and small artery bleeding is in the range of 3.3-30% (10). The evolution of hemostasis during the last few centuries of surgical history has resulted from the development of hemostatic agents and devices, as well as surgical skills and principles (1). Moreover, different types of bleeding occur, and appropriate methods should be applied in each situation. Several materials have been devised to control bleeding by understanding the mechanisms of the hemostatic process (11,12).

➔ Page 10)

Although randomized controlled trials have investigated the efficacy and safety of ORC as a topical hemostatic agent (31), the present study was based on a large cohort focusing on the clinical effectiveness of ORC-derived material in multiple clinical surgery departments. In previous studies, the SurgiGuard® shown to be effective and safe in porcine models. Based on these favorable results, a large-cohort multicenter

collaborative study was designed and conducted.These results evaluated and reported from the perspective of surgeons who used topical hemostasis agents themselves may be a milestone for more surgeons who will use these materials in the future.

However, ORC hemostatic agents have several side effects. ORC has been reported to dissolve promptly at various sites in an animal experiment within 6 weeks (32). In contrast to the animal model, several case reports have presented that the residue of ORC could easily be mistaken for an abscess or granuloma on postoperative imaging (33). For this reason, some clinicians have suggested that ORC should be used in extreme care for rigid non-extensive anatomical structures and be removed after hemostasis as soon as possible (34).

Despite encouraging results, this study has certain limitations. First, this study was based on a survey that received responses from a surgeon who performed various surgeries. Thus, one of the main challenges of this study is that the results reflect subjective points of view and experiences. the degree of bleeding Second, due to the heterogenousity of the analyzed study group, we did not sufficiently investigate the unique characteristics of each surgey. In the same context, the degree of bleeding was not accurately assessed using the confirmed bleeding scale VIBe SCALE (validated intraoperative bleeding scale) (35). Third, this study was focused on a short-term outcome survey, and it was not possible to investigate long-term complications, such as abscess or mass-like foreign body, the most common complication of ORC-derived hemostatic agents. As various surgeries and divisions were included, the endpoint of this study was unclear. Further studies, such as head-to-head, randomized controlled cohorts, are required to investigate not only short-term but also long-term complications, taking into account the characteristics of each surgery. Moreover, research on which type of SurgiGuard® is useful and effective under what circumstances should be accompanied.

Author's response to Reviewer D

i would concur that ORC is useful for the bleeding surgical field.
it is very challenging to statistically quantify the effectiveness of a hemostatic agent, and i would congratulate the manuscript team for providing some statistical analysis on this.
Unfortunately, i am unable to see how this manuscript provides new/useful information about ORC hemostatic agents that we do not already know. Please kindly elaborate on how the information presented in this paper adds useful knowledge on ORC hemostatic agents.

i am unable to see how this paper provides new/useful information about ORC hemostatic agents that we do not already know.
- Statistical analysis is purely descriptive in nature; it does not provide useful data to suggest how ORC hemostatic agents are useful.

➔ We appreciate your thoughtful comments. As the reviewer has pointed out, we are aware that it is challenging to quantify the effectiveness of a hemostatic agent such as SurgiGuard. We are also aware that many hemostatic agents are already being used in various clinical fields. ORC-derived hemostatic agents were introduced several decades ago, and most aspects of these products have been investigated and reported. In addition, several randomized controlled trials have been conducted. Nonetheless, the present study is the only report that focuses on clinical effectiveness through largest-cohort multicenter in various surgical departments. We believe that the results of this study will provide objective clinical stability for surgeons using this product. Our team previously reported on the safety and feasibility of this product in a porcine model; the series of processes that we have presented will provide clinicians with reliability. (Kim, S. H., et al. (2016). "Efficacy of the SurgiGuard in partially hepatectomized pigs Korean journal of hepato-biliary-pancreatic surgery 20(3): 102-109.) (Kim, S. H., et al. (2017). "Efficacy of Oxidized Regenerated Cellulose, SurgiGuard®, in Porcine Surgery." Yonsei medical journal 58(1): 195-205.) Fully reflecting these comments, we have explained the mechanism, limitations, and meaning of this study in the Discussion section.

➔ Page 10)

Although randomized controlled trials have investigated the efficacy and safety of ORC as a topical hemostatic agent (31), the present study was based on a large cohort focusing on the clinical effectiveness of ORC-derived material in multiple clinical surgery departments. In previous studies, the SurgiGuard® shown to be effective and safe in porcine models. Based on these favorable results, a large-cohort multicenter collaborative study was designed and conducted.These results evaluated and reported from the perspective of surgeons who used topical hemostasis agents themselves may

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Despite encouraging results, this study has certain limitations. First, this study was based on a survey that received responses from a surgeon who performed various surgeries. Thus, one of the main challenges of this study is that the results reflect subjective points of view and experiences. the degree of bleeding Second, due to the heterogenousity of the analyzed study group, we did not sufficiently investigate the unique characteristics of each surgey. In the same context, the degree of bleeding was not accurately assessed using the confirmed bleeding scale VIBe SCALE (validated intraoperative bleeding scale) (35). Third, this study was focused on a short-term outcome survey, and it was not possible to investigate long-term complications, such as abscess or mass-like foreign body, the most common complication of ORC-derived hemostatic agents. As various surgeries and divisions were included, the endpoint of this study was unclear. Further studies, such as head-to-head, randomized controlled cohorts, are required to investigate not only short-term but also long-term complications, taking into account the characteristics of each surgery. Moreover, research on which type of SurgiGuard® is useful and effective under what circumstances should be accompanied.