Journal of Surgery
Nowrouzi R and Awad SS. J Surg 8: 1918
www.doi.org/10.29011/2575-9760.001918
www.gavinpublishers.com
Research Article

Activated Collagen Powder Significantly Reduces Surgical Site Infections in Patients Undergoing Elective Surgery

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Citation: Nowrouzi R, Awad SS (2023) Activated Collagen Powder Significantly Reduces Surgical Site Infections in Patients Undergoing Elective Surgery. J Surg 8: 1918 DOI: 10.29011/2575-9760.001918

Received Date: 19 October, 2023; **Accepted Date:** 23 October, 2023; **Published Date:** 25 October, 2023

Abstract

Objective: Surgical Site Infections (SSI) are common hospital infections resulting in morbidity, mortality, and cost. Activated Collagen (AC) has been shown to promote wound healing, preventing wound dehiscence with decrease in SSIs. We evaluated the impact of AC on SSI rates in elective surgery patients.

Methods: We conducted a retrospective review of surgery patients from 1-1-2018 to 12-1-2021. Comorbidities, demographics and surgical specialties were collected. All patients had chlorhexidine wipes day prior and on day of surgery; appropriate prophylactic antibiotics; and ChloraPrep or DuraPrep. AC (CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth TX) was applied prior to skin closure. Cases were stratified by wound class. AC group patients were compared to case matched 1:3 non-AC patients. SSI rates were compared.

Results: 5,335 cases were performed, 76% (4,068) clean, 24% (1,287) Clean Contaminated (CC). Overall, the mean age was 63.8+/-0.9 years, mean BMI was 28.8+/-0.44; 87% male, 56% white, 31% with DM, 13% with CKD, and 7% with COPD. The AC and Non-AC groups were well matched with no significant differences in age, BMI, demographics, comorbidities or surgical specialty. AC was used in 28% (Total=1489; Clean=1,089; CC=400) of cases. There was a significant decrease in overall SSI rate with use of AC (AC SSI=0.63%, Non-AC SSI= 1.52%, p=.012). There was a significant decrease in SSI rate in clean cases (AC SSI=0.30%, Non-AC SSI=0.97%, p=.027) and trend towards decreased SSI rate in clean contaminated cases (AC SSI=1.54%, Non-AC SSI=3.36%, p=.064)

Conclusions: AC in patients undergoing elective surgery resulted in a significant 59% reduction in SSI rate; most pronounced in clean cases (69% decrease). Activated collagen can be safely used in elective cases to promote wound healing of incisions and decrease SSI rates.

Keywords: AC; Activated Collagen; Elective Surgery; SSI; Surgical Site Infection

Introduction

Surgical Site Infections (SSIs) are among the most common preventable complications after surgery and constitute a significant source of morbidity, mortality and cost in the postoperative period. [1,2] AHRQ data demonstrates that SSIs occur in 2% to 4% of all patients undergoing inpatient surgical procedures and approximately 3% of patients who contract an SSI will die as a consequence. Despite the use of evidence-based practices, national guidelines, and incentives to reduce SSI rates, more than half of all SSIs continue to occur because of patient and facility level factors that have been shown to increase SSI risk. [3,4]

Patients who develop SSIs have increased health care utilization, including increased length of hospital stay, emergency department visits, readmissions, and outpatient visits resulting in increased morbidity, and mortality with resultant increased financial costs to providers and payers [5,6].

Collagen is the most abundant protein in the human body. Type I collagen plays a pivotal role in wound healing. It is the major component of the extracellular matrix and has been shown to support wound healing through chemotaxis with cell migration, promoting tissue ingrowth and ultimately remodeling to provide wound tensile strength. Native collagen is an insoluble, rigidly coiled helical molecule that is critical to wound healing and one of the first tissue structures deposited into the wound base by fibroblasts. Collagen must then be hydrolyzed by proteases such as various collagenases, and matrix metalloproteinases into its soluble component amino acid peptides in order to realize additional biological benefits. Activated Collagen Peptides (AC) result from the conversion of the coiled collagen helix into peptides which support the cellular activities and migration associated with granulation, angiogenesis and re-epithelialization. [7] Activated collagen has been shown to promote wound healing and prevent wound dehiscence. [8,9] In addition, in vitro, hydrolyzed collagen has demonstrated antibacterial activity against *Escherichia coli, Bacillus subtilis* and *Staphylococcus aureus*. [10] MIC studies have demonstrated that activated collagen has been shown to significantly retard gram positive bacterial growth with a Zone of Inhibition (ZOI) comparable to vancomycin (ZOI=8 mm). Although no discrete ZOI was identified for gram negative bacteria, there was some noted inhibition (Figure 1). Interestingly, AC has antioxidant and antimicrobial activities. Hydrogel preparations of AC were shown to have antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. These preparations were also shown to promote cell proliferation and migration and burn wound healing. [8] Given the wound healing characteristics of activated collagen and the potential observed bacterial retardation observed, the aim of the present study was to determine the impact of activated collagen on surgical site infection rates on patients undergoing elective surgery across multiple surgical specialties. We hypothesized that activated collagen would decrease SSIs in patients undergoing elective surgery.

NELSON LABORATORIES

Laboratory Number 828390
Antimicrobial Susceptibility Test - Zone of Inhibition Final Report

Results:
Zone of Inhibition Measurement:

Organism	Identification	Diameter Of The Zone Including Test article (mm)
S. aureus	1	7.29
	2	8.20
	3	9.07
	Control 1	No Zone
	Control 2	No Zone
	Control 3	No Zone
P. aeruginosa	1	No Zone[a]
	2	No Zone[a]
	3	No Zone[a]
	Control 1	No Zone
	Control 2	No Zone
	Control 3	No Zone
S. agalactiae	1	No Zone
	2	No Zone
	3	No Zone
	Control 1	No Zone
	Control 2	No Zone
	Control 3	No Zone
E. coli	1	No Zone
	2	No Zone
	3	No Zone
	Control 1	No Zone
	Control 2	No Zone
	Control 3	No Zone
S. epidermidis	1	9.13
	2	9.93
	3	8.76
	Control 1	No Zone
	Control 2	No Zone
	Control 3	No Zone
P. vulgaris	1	No Zone[a]
	2	No Zone[a]
	3	No Zone[a]
	Control 1	No Zone
	Control 2	No Zone
	Control 3	No Zone

[a] A reduction in growth was observed but no clear zones formed.

Figure 1: *In vitro*, AC (CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth TX) has been shown to significantly retard gram positive bacterial growth with a zone of inhibition (ZOI) comparable to vancomycin (ZOI=8 mm).

Methods

Under a Baylor College of Medicine IRB approved protocol, a retrospective review of a prospective data base of patients undergoing elective surgery at a tertiary academic hospital was performed from 1-1-2018 to 12-1-2021. Age, gender, race, and comorbidities such as diabetes mellitus, BMI, chronic kidney disease, chronic obstructive pulmonary disease, malnutrition, immunosuppression, and tobacco use were collected. Surgical specialties included general, surgical oncology, orthopedic,

vascular, neurosurgery, cardiothoracic, plastic and gynecology. All patients underwent preoperative decontamination with chlorhexidine wipes on the day prior and on the day of surgery. All patients had surgery site appropriate prophylactic antibiotics prior to incision. Prior to incision, the skin was prepped with either ChloraPrep or DuraPrep. In the activated collagen group, AC ((CellerateRX® Surgical Powder, Sanara MedTech, Fort Worth TX)) was applied in the subcutaneous tissue prior to skin closure. Cases were stratified as clean (CL) or Clean Contaminated (CC). Contaminated or infected surgical procedures were excluded. Patients in the AC group (n=1,489) were compared to case matched Non-AC patients (n=3846). 30-day SSI rates were calculated for each group. Student's t-test was used to compare continuous data. Chi square analysis was used to compare SSI rates between groups using $p<0.05$ as significant. In order to account for the differences in infection risk, a sub-analysis was performed to distinguish the efficacy of activated collagen in patients undergoing clean cases as well as clean-contaminated cases.

Results

Between 2018 and 2021, a total of 5,335 surgeries were performed: 4,068 (76%) were clean (CL) and 1,287 (24%) were Clean-Contaminated (CC). Overall, the mean age was 63.8+/- 0.9 years, and the mean BMI was 28.8 +/-0.44. 87% were male, 56% were white, 31% with DM, 7% with history of COPD, 13% with chronic kidney disease, and 31% with active tobacco use. The AC and Non-AC groups were well matched with no significant differences in age, BMI, gender, race, comorbidities or surgical specialty. Overall AC was used in 28% (Total=1489; CL=1089; CC=400) of elective cases. There were more clean cases performed in the Non-AC group (77% vs 73%, p=0.22) and more clean contaminated cases performed in the AC group (27% vs 23%), p=0.024). There was a significant decrease in overall SSI rate with use of AC (AC SSI=0.63%, Non-AC SSI= 1.52%, p=.012). There was a significant decrease in SSI rate in clean cases (AC SSI=0.30%, Non-AC SSI=0.97%, p=.027) and a trend towards decreased SSI rate in clean contaminated cases (AC SSI=1.54%, Non-AC SSI=3.36%, p=.064) (Table 1). The use of activated collagen in patients undergoing elective surgery resulted in a significant 59% reduction in SSI rate. This was most pronounced in the clean cases with a 69% decrease in SSI rate.

	Overall (n=5335)	Non-AC (n=3846)	AC (n=1489)	p value
Age (years)	63.8 +/- 0.9	65.2 +/- 1.1	62.5 +/- 1.4	0.13
BMI (kg/m²)	28.8 +/- 0.44	29.04 +/- 0.6	28.53 +/- 0.7	0.56
Gender				0.35
Male	4627 (87%)	3346 (87%)	1281 (86%)	
Female	708 (13%)	500 (13%)	208 (15%)	
Race				0.87
Black	1877 (35%)	1342 (35%)	535 (36%)	
Hispanic	214 (4%)	154 (4%)	60 (4%)	
White	3002 (56%)	2153 (56%)	849 (57%)	
Other	242 (5%)	197 (5%)	45 (3%)	
DM	1673 (31%)	1223 (32%)	450 (31%)	0.27
COPD	386 (7%)	267 (7%)	119 (8%)	
CKD	679 (13%)	500 (13%)	179 (12%)	
TOB	1668 (31%)	1192 (31%)	476 (32%)	
Cases				
CL	4068 (76%)	2979 (77%)	1089 (73%)	0.22
CC	1287 (24%)	887 (23%)	400 (27%)	0.024
SSI Rate				
Overall	68 (1.3%)	59 (1.52%)	9 (0.63%)	0.012
CL	32 (0.79%)	29 (0.97%)	3 (0.30%)	0.027
CC	36 (2.8%)	30 (3.36%)	6 (1.54%)	0.064

Categorical variable data expressed as n (%); Continuous data expressed as MEAN +/- SEM; SSI= 30-day Surgical Site Infection, BMI= body mass index, DM= Diabetes Mellitus, COPD= Chronic Obstructive Pulmonary Disease, TOB= Active tobacco Use, CKD= Chronic Kidney Disease, CL= Clean, CC= Clean Contaminated

Table 1: Baseline characteristics & SSI Rate.

Discussion

Surgical site infections remain a significant cause of morbidity and mortality in the post-surgical patient. Given the increasing number of complex surgeries and the increasing age and comorbidities of patients, the implementation of guidelines and interventions to reduce SSIs is crucial to preventing an increase in SSI-related complications and health care utilization and has been advocated by several major healthcare organizations. [11] These interventions include smoking cessation, optimizing preoperative nutrition and diabetes management, skin decontamination with preoperative chlorhexidine wipes, appropriate surgery specific prophylactic antibiotic use, patient warming, meticulous surgical technique, attentive postoperative monitoring, modern wound closure dressings, and closed-incision negative pressure therapy. [11,12] Many of these practices are included in Enhanced Recovery After Surgery (ERAS) protocols which have been associated with reductions in post-operative complications, surgical site infections, length of stay and costs. [13-16] Despite all these efforts to reduce the incidence of these infections, the rates of SSIs still remain high especially for open surgeries. [3] The impact of surgical site infections on health care utilization is high with significant increase in cost secondary to the treatment of the acquired infection which results in additional length of stay, the preventable readmissions and the need for additional surgeries. When the SSI results in a prosthetic infection, the health care costs are even higher. Hou et al. reported an average of 9.3 (95% CI: 9.2-9.3) additional LOS for Medicare patients with an estimated cost of $18,626 (95% CI: $18,484-$18,771) for superficial infections. In contrast, Deep SSIs resulted in an average of 11.4 days and $24,503. Given the morbidity, increase in the risk of mortality and health care costs when surgical site infections occur, additional interventions such as the placement of products that can promote wound healing and sealing especially in high-risk patients and retard any bacterial overgrowth in the immediate postoperative setting would potentially be worthwhile.

Collagen constitutes a major component of the cellular extracellular matrix and has been shown to support wound healing in three distinct ways including cell migration to injured tissue, new tissue ingrowth, and support of wound tensile strength. Activated collagen that is commercially available is produced from the enzymatic cleavage of type I bovine collagen resulting in peptides that then confer biological activity.[7] The use of activated collagen intraoperatively, in conjunction with the implementation of the strategies described above, can further produce the benefit of expedited wound healing with the potential of retarding bacterial growth in patients with significant comorbidities that impact wound healing and increase surgical site infection risk; thereby potentially decreasing the rate of surgical site infections. Figure 1 demonstrates that *in vitro,* the activated collagen used in this study retards gram positive bacterial growth with a zone of inhibition similar to vancomycin. In addition, activated collagen demonstrated decreased growth of gram-negative bacteria. The mechanism behind its bacterial retardant properties has yet to be elucidated, however the role of collagen in during the inflammatory phase of wound healing, which begins as soon as an incision is made, has been widely studied. In the inflammatory phase of wound healing, activated collagen is involved mitigating the inflammatory response, serves as a potent chemokine for immune cell activation, promotion of angiogenesis, and re-epithelialization of the healing surgical wound all of which occur through complex molecular pathways. [17] Specifically, during the inflammation phase, the soluble fragments of activated collagen recruit immune cells such as macrophages that patrol the wound for removal of microbes and devitalized tissue. In an excisional murine dermal model, activated collagen 100mg/wound, was applied and compared to untreated controls. The addition of the activated collagen resulted in boosted phagocytosis, and efferocytosis of the wound site macrophages with higher inducible reactive oxygen species by day seven. In addition, activated collagen potentiated expression of anti-inflammatory IL-10 cytokine and VGEF production by day ten [9].

Clinically, there have been few reports of the use of activated collagen. Most of the studies focus on the promotion of wound healing of open wounds. Shapiro et al. examined the use of activated collagen in 16 patients, eight with activated collagen + Standard of Care (SOC) and eight with SOC only. At 14 weeks, the patients that received activated collagen had 100% of their DFUs healed compared to 13.5% in the SOC only group. [18] Additionally, Gitelman demonstrated in a series of 54 consecutive patients that hydrolyzed collagen powder used in patients undergoing spinal surgery to correct spinal deformity or treat spinal fractures had no SSIs or wound dehiscence between two and six weeks post-surgery. [19] Our study is the first to examine the use of activated collagen in clean and clean contaminated elective surgery in various subspecialties and surgical sites and compare the 30-day SSI rate to case matched controls. Our results demonstrate that the use of AC demonstrated significantly decreased SSI rates which was most pronounced in clean cases; most of which are typically caused by gram positive bacteria. This clinical observation is consistent with the observed bacterial retardation seen in vitro and the reported antibacterial effects of gram-positive and gram-negative bacteria in animal models. This bacterial retardation along with boosted phagocytosis, efferocytosis, increase in reactive oxygen species, and mitigation of the inflammatory response may have contributed to the observed significant decrease in SSIs in our study.

Limitations

This is a retrospective study with inherent limitations, including the inability to adjust for unobserved covariates, a predominantly male, Caucasian population and a higher proportion of clean cases. Although the placement of the activated collagen in the AC group was confirmed, the specific amount placed was not measured with variability secondary to surgeon preference among the different specialties. In addition, there may have been variability with the skin closure technique and dressings applied.

Conclusion

Activated collagen can be safely used in elective surgical procedures to promote wound healing of incisions as well as decrease the rate of SSIs following surgery. Further studies are required in order to better elucidate the mechanism of action of activated collagen that resulted in the observed decrease in surgical site infections.

Funding Statement: Supported by Investigator Initiated Grant, Wound Management Technologies Inc.

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