










Effects of hyaluronic acid and chondroitin sulfate on acute radiation proctitis in rats

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ABSTRACT

BACKGROUND: This study was designed to investigate the prophylactic and therapeutic effects of hyaluronic acid and chondroitin sulfate combination (HA/CS) on a model of acute radiation proctitis.

METHODS: Rats were divided into five groups: SHAM; irradiation (IR) + saline (1 mL for 5th and 10th day); IR + HA/CS (1 mL for 5th and 10th day). A single fraction of 17.5 Gy was delivered to each rat. HA/CS was administered rectally each day after irradiation. Each rat was observed daily for signs of proctitis. Irradiated rats were euthanized on days 5 and 10. The mucosal changes were evaluated macroscopically and pathologically.

RESULTS: According to the clinical findings, five rats in the irradiation + saline group showed grade 3–4 symptoms on the 10th day. No significant difference in the macroscopic finding scores on the 5th day was observed between the irradiation + saline and irradiation + HA/CS groups. In the pathological examination, radiation-induced mucosal damage was the most prominent finding 10 days after irradiation in saline-treated rats. On the 10th day, the irradiation + HA/CS group showed mild inflammation and slight crypt changes, which corresponded to grade 1–2 pathological findings.

CONCLUSION: We think that HA/CS used in radiation cystitis can be beneficial for radiation proctitis.

Keywords: Chondroitin sulfate; hyaluronic acid; radiation proctitis.

INTRODUCTION

Acute and late radiation-induced cystitis and proctitis are side effects seen in 25–40% of patients with pelvic organ cancer treatment during and after radiotherapy (RT).^[1] RT has an importance in managing malignancies of pelvic organs. Because of the rectum location in the pelvic and its anatomical relationship with pelvic organs may cause secondary radiation injuries such as proctitis.^[2] Acute or chronic damage can be

by radiation. Acute radiation proctitis (ARP) is observed in during RT or up to 6 weeks after completion of RT, at 50–75% of patients, and after 2–6 months symptoms of radiation injury decrease. Symptoms of ARP include diarrhea, abdominal pain, nausea, intermittent bleeding, constipation, mucus discharge, or some urinary symptoms. Ulceration, inflammation, mucosal edema, crypt disintegration, epithelial degeneration, crypt abscesses, and absent mitosis are the histopathological changes found in ARP.^[3] In the literature, animal exper-

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iments have used many drugs that are thought to prevent radiation damage, including ozonated olive oil, sildenafil, and ruscofenin.^[4-6] Hyaluronic acid (HA) and chondroitin sulfate (CS), which are components of the urothelial mucosa layer. Intravesical HA and chondroitin sulfate combination (HA/CS) (iAluRil®, Aspire Pharma) are applied in the treatment of urinary tract infections and bladder pain syndrome.^[7] HA/CS is thought to benefit RT bladder toxicity with a protective therapeutic effect on the bladder.^[8,9] Therefore, the aim of this study is to determine whether the HA/CS used in radiation cystitis is also effective in ARP.

MATERIALS AND METHODS

The approval of Ege University Animal Research Committee was obtained for the experimental protocols with approval number 2015–079.

Animals

Thirty Wistar albino rats, 6 weeks old, weighing 200–240 g, were taken from EGE University Experimental Medicine Institute. All animals were acclimatized for 7 days before experiments in the institute's laboratory. Before and after the experiments, the rats were placed in cages with chow and water. Animal rooms had no windows, temperature (22°C±2°C) and light were under control. The night before the experiments were conducted, the animals were starved, but water was free.

The rats were divided into three groups randomly as those with the IR + saline group (saline group, 12 rats), the IR + HA/CS group (HA/CS group, 12 rats), and the control group (6 rats). A single dose of 17.5 Gy was irradiated to the pelvic region in both the saline group and the HA/CS group. In the HA/CS group, 1 mL HA/CS was given intrarectally once a day from the beginning of the radiation day to until the euthanasia. Saline was administered to the same protocol to the saline group. In the control groups', rats were administered no saline or HA/CS.

Pelvic Irradiation

Before IR, each rat was anesthetized intramuscularly with 5 mg/kg xylazine and 30 mg/kg ketamine hydrochloride. Afterward, 3–4 rats were taken and taped supine from their tails and legs onto an acrylic plate. An area of the lower pelvic region measuring 3×3 cm, including the 2 cm long rectum, was determined for radiation, and 6 MV linear enhancer IR is provided. On the irradiated area, bolus material was placed and a single dose of 17.5 Gy was administered to each rat. It is known that the IR dose, given is the optimal dose in producing clinical proctitis.

Treatment with HA/CS

HA/CS, prepared to be the same as body temperature. 1 mL HA/CS was administered once a day from 1st day of IR ad-

ministration until euthanasia. HA/CS was given with catheter; then, the anus was closed with manual compression for 4–5 min.

Evaluation of Rectal Damages

Each rat was checked for marks of proctitis daily after IR (diarrhea or rectal bleeding etc). Score classification of the clinical findings: 0, do not symptoms; 1, restlessness (weakness and reduce appetite); 2, diarrhea; 3, diarrhea and minimal bleeding; and 4, gross bleeding. Euthanasia days were determined according to studies conducted at various times.^[3-6] Six rats were euthanized on 5th and 10th day after IR administration, and histological and macroscopic findings evaluated. Euthanasia was performed surgically with cardiac blood loss by administering 100 mg/kg ketamine hydrochloride and 20 mg/kg xylazine anesthesia. After the incision in the middle, the small and large bowel was removed. The pelvic symphysis was cut and elevated to reach the distal rectum and anus. A 2 cm of the anal part of the distal rectum was excised. Macroscopic classification of the rectum: 0; normal mucosa, 1; edema, decreased vascularity, or mild hyperemia, 2; diffuse hyperemia, multiple punctuated surfaces of hemorrhage, or confluent surfaces of hemorrhage, 3; the presence of erosions or frank hemorrhage, and 4; ulcers. Histological preparation: all specimens were fixed in 10% formol solution. Then, the specimens were embedded in paraffin blocks and cut into 5-micron longitudinal sections. Samples were stained with hematoxylin-eosin, histopathological evaluation under the light microscope was examined by a pathologist. Pathological classification: normal or minor alterations (grade 0); mild inflammation and/or changes of crypt (grade 1); more significant inflammation and/or slight crypt change (grade 2); variable degree of inflammation and/or regenerative/restorative atypia of epithelial cells (grade 3); and ulcer and/or necrosis (grade 4).

Statistical Analysis

Data analysis was implemented using the Statistical Package for the Social Sciences version 24. The Kruskal–Wallis method was used for more than two groups in the comparison of numerical variables between groups. Bonferroni or Mann–Whitney U-test was performed after multiple analyses. $P < 0.05$ was considered significant at the 95% confidence interval.

RESULTS

28–30 rats were included in the study. Two rats were excluded because they died due to complications of anesthesia. The remaining four rats were examined in the sham group.

Only one rat from the IR + HA/CS group was healthy on the 5th day after IR, with a clinical finding score of grade 0. In the evaluations on the 5th day after IR, Grade 1–2 symptoms were seen in 9 rats. Five rats with Grade 1–2 symptoms were in the saline group, and 4 rats with Grade 1–2 symptoms were in the HA/CS group. On the 10th day groups, Grade 3–4

Table 1. Clinical findings of groups

	5 th day			10 th day			
	SHAM (n=4)	IR+saline group (n=6)	IR+HS/CS Group (n=6)	p	IR+saline group (n=6)	IR+HS/CS group (n=6)	p
Grade 0	4	0	1	0.09	0	0	1
Grade 1		2	2	1	1	2	0.08
Grade 2		3	2	0.085	0	3	0.002*
Grade 3		0	1	0.086	3	1	0.001*
Grade 4		1	0	0.087	2	0	0.001*

IR: Irradiation; HS/CS: Hyaluronic acid and chondroitin sulfate combination *P<0.05

symptoms were noted in 6 rats. Five rats in the saline group and 1 rat in the HA/CS group had Grade 3–4 symptoms. The incidence of Grade 3–4 symptoms was higher on the 10th day in the saline group. There was a statistically significantly different between the other groups with the saline group (P=0.001). The clinical findings of the groups are shown in Table 1.

The mean clinical finding score was 1.5 ± 0.28 and 1.6 ± 0.30 in the HA/CS and in the saline group on the 5th day following IR, respectively (P=0.1), on the 10th day was $1.83\pm 0.34/3\pm 0.43$, respectively (P=0.005).

In macroscopic examinations, grade 0 was only 2 rats in the HA/CS group on the 5th day. On the 5th day after IR, 4 rats in the saline group and 3 rats in the HA/CS group had grade 1–2 macroscopic findings, the results of both groups were similar and the difference between the groups on the 5th day after IR did not statistical significance. On the 10th day after IR, grade 1–2 macroscopic findings were observed in the same number of rats in both groups. Grade 4 macroscopic findings did not seen in IR + HA/CS group on the 5th day and 10th days. The macroscopic findings are listed in Table 2.

The mean macroscopic finding score was 1.16 ± 0.22 and

1.5 ± 0.34 in the HA/CS group and in the saline group on the 5th day following IR, respectively (P=0.08), on the 10th day was 1.83 ± 0.32 and 2.83 ± 0.43 , respectively (P=0.008).

Histopathological changes were highest in the IR + saline 10th-day group. It was characterized by epithelial loss and mucosal ulceration through the muscularis mucosa. Changes in post-IR day 5 samples were mild–moderate inflammation and mild crypt disruption. Histopathological changes on the 5th day after IR were milder than on the 10th day after IR in the saline group, but there was no significant difference. In the HA/CS group, on the 5th and 10th days had no Grade 4 pathological finding. There was a statistically significant difference between the groups (P=0.001). The pathological findings are listed in Table 3.

The mean of the pathological finding score was 2.83 ± 0.43 on the 5th day and 3.33 ± 0.47 on the 10th day in the saline group. In HA/CS group, on the 5th day, the pathological finding score was 1.66 ± 0.28 , on the 10th day, the pathological finding score was 2 ± 0.23 . On the 10th day, there was a statistically significant difference in the pathological findings in the saline group compared to the HA/CS group (P=0.003). Clinical, macroscopic, and pathological findings comparison are listed in Table 4.

Table 2. Macroscopic findings

	5 day			10 day			
	SHAM (n=4)	IR+saline group (n=6)	IR+HS/CS Group (n=6)	p value	IR+saline group (n=6)	IR+HS/CS group (n=6)	p value
Grade 0	4	0	2	0.001	0	0	1
Grade 1		3	2	0.19	1	2	0.06
Grade 2		1	1	0.99	2	3	0.09
Grade 3		2	1	0.09	0	1	0.09
Grade 4		0	0	0.99	3	0	0.001*

IR: Irradiation, HS/CS: Hyaluronic acid and chondroitin sulfate combination. *P<0.05

Table 3. Pathological findings in the groups

	SHAM (n=4)	5 th day			10 th day		
		IR+saline group (n=6)	IR+HA/CS Group (n=6)	p value	IR+saline group (n=6)	IR+HA/CS group (n=6)	p value
Grade 0	4	0	0	1	0	0	0.99
Grade 1		0	1	0.08	0	2	0.07
Grade 2		2	3	0.09	1	2	0.6
Grade 3		3	1	0.05	2	2	0.9
Grade 4		1	0	0.08	3	0	0.001*

IR: Irradiation; HA/CS: Hyaluronic acid and chondroitin sulfate combination *P<0.05

Table 4. Comparison of the clinical, macroscopic, and pathological finding scores mean between the groups

Groups	Clinical finding score	P-value	Macroscopic finding score	P-value	Pathological finding score	P-value
IR+Salin 5 th day	1.6±0.30	0.1	1.5±0.34	0.08	2.83±0.43	0.06
IR+HA/CS 5 th day	1.5±0.28		1.16±0.22		1.66±0.28	
IR+Salin 10 th day	3±0.43	0.005*	2.83±0.43	0.008*	3.33±0.47	0.003*
IR+HA/CS 10 th day	1.83±0.3		1.83±0.32		2±0.23	

IR: Irradiation; HA/CS: Hyaluronic acid and chondroitin sulfate combination *P<0.05

DISCUSSION

Pelvic RT is the most common definitive treatment method after surgery in moderate and low-risk prostate cancers, and the most common side effect is damage to neighboring organs, such as acute radiation cystitis (ARC) and ARP. In ARP and ARC, an inflammatory reaction is observed in the superficial mucosa and submucosa.^[10] ARP and ARC may occur up to 3 months after the initiation of therapy. Late radiation cystitis and proctitis can be seen up to 10 years after pelvic RT.^[11] The symptoms of ARP, including nausea, urgency, diarrhea, tenesmus, mucus discharge, and minor or life-threatening bleeding, ARP symptoms occur in 20% of patients.^[12] Some studies have been made to identify the best strategy for preventing or treating ARP and ARC symptoms. RT results in oxidative stress, and free oxygen radicals have been play an essential role in radiation-induced toxicity to the mucosal layer and inflammation. Increased levels of antioxidant enzymes can inhibit mucosal layer replacement, prevent IR from damaging healthy tissues, and reduce inflammation.^[12,13]

The epithelial barrier consists of a protective mucin layer. The main components of the mucin layer are HA and CS glycosaminoglycans. CS is a natural macromolecule and belongs to the class of glycosaminoglycans. Sulfate is known as an antioxidant molecule. HA/S application is beneficial in the treatment of inhalation burns and ARC.^[13-15] It could be applied through rectal, topical, and intravesical routes. HA/CS administration has been used in the treatment of recurrent urinary tract

infection and interstitial cystitis and there are many studies, but there are limited and insufficient studies on the use of intravesical HA/SC in the treatment of radiation-induced cystitis.^[13,14] All studies on HA/CS have focused on treating radiation-induced cystitis; however, no studies have examined the therapeutic effects of HA/CS on radiation proctitis. There are animal studies, in which many substances were used intrarectally to prevent radiation proctitis, one of which are ozone, ozonated olive oil, polaprezinc, or ruscogenin.^[16] There is no study in the literature on the effects of HA/CS on ARP in animals or humans. This could be the first study about the effect of HA/CS. In this study, we investigated the effects of HA/CS on rats with radiation proctitis clinically, macroscopically, and histopathologically.

Regarding clinical findings, the lowest symptom score was observed in the HA/SC group 5 days after IR, and the highest symptom score was observed in the saline group on the 10th day after IR. Grade 4 symptoms were observed in one rat on the 5th day and two rats on the 10th-day saline group, whereas these symptoms were not observed in any rat receiving HA/SC. On the 10th day after IR in the two groups, significant differences in the clinical findings were found (P=0.001). It was observed that HA/CS did not affect mild symptoms but reduced severe symptoms.

In general, ARP is an inflammatory process of mucosa epithelial layer. The macroscopic findings, it has been reported in many studies that the macroscopic appearance of inflammation

starts on the 6th day after IR and progresses to multifocal ulceration with severe inflammation on the 10th day.^[17] In our study, macroscopic changes were evaluated in the specimens on the 5th and 10th days after IR, and the findings were similar to previous studies. We could show that the intrarectal application of HA/CS for 10 days improved the macroscopic mucosal changes of ARP, and the difference was significant for the grade 4 finding (P=0.001).

Pathological findings of mucosal damage in the rectum in our study were mucosal ulceration, epithelial loss, crypt changes, and necrosis, which were consistent with previous studies.^[17,18] Pathological differences were more pronounced at day 10 in the saline group. The HA/CS group had lower scores than the saline group on the 10th day and the difference for grade 4 findings was statistically significant.

In our study, in all evaluations of rats, it was observed that tended to show milder rectal damage in the HA/CS group than in the saline group. In the clinical, macroscopic, and pathological findings, scores on the 5th day were not statistically significant between the two groups. However, on the 10th day, clinical, macroscopic, and pathological findings, scores in the saline group were significantly higher than in the HA/CS group. Moreover, on the 10 day, HA/CS treatment appeared to be more effective than on the 5-day HA/CS treatment after IR. The effects of HA/CS on ARP were observed to be beneficial.

In the literature, the efficacy of various agents in the treatment of radiation side effects has been investigated. Due to the proven benefits of using HA/CS in the treatment of radiation-induced cystitis, we also considered using it in radiation-induced proctitis. It has been emphasized that ozone used in the treatment of resistant hemorrhagic radiation proctitis is beneficial. It has been reported that intraperitoneally administered ozone also protects against radiation-induced mucosal damage of the intestine.^[18] Ozone protects to increase endogenous antioxidant enzymes and inhibition of lipid peroxidation. We believe that the sulfate bonds in HA/CS reduce free oxygen radical damage using the same mechanism of action as in ozone. Doi et al. applied intrarectal polaprezinc in rats and reported that it slowed down the development of ARP.^[19] Similarly, another study reported that high-dose Triphala treatment with oral application improved radiation-induced acute intestinal mucosal damage in rats.^[20] In addition, IR causes damage to endothelial cells and results in hypoxemia.^[21] HA/CS provides mucosal healing by decreasing the oxidative reaction and increasing the oxygen tension. The increase in oxygen tension in the wound increases the granulation tissue and wound healing accelerates.^[22] In the treatment with HA/CS, the new epithelialization process is accelerated with a similar mechanism. However, further studies will contribute to the literature to investigate the beneficial effects of HA/CS treatment.

Conclusion

There are many studies on the use of HA/CS in the treatment of radiation cystitis. We tried to prove that HA/CS can be used in radiation proctitis in rat models. We have demonstrated the therapeutic and prophylactic effect of HA/CS, a combination of CS and HA, in preventing ARP.

Ethics Committee Approval: This study was approved by the Ege University Animal Experiment Ethics Committee (Date: 25.11.2015, Decision No: 2015-079).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.Y., T.Y.; Design: M.Y., T.Y., İ.S., C.Ç., S.C., B.D., M.S., S.A., T.K.Y.; Supervision: M.Y., T.Y., İ.S., C.Ç., S.C., B.D., M.S., S.A., T.K.Y.; Fundings: M.Y., T.Y., İ.S., C.Ç., S.C., B.D., M.S., S.A., T.K.Y.; Materials: M.Y., T.Y., İ.S., C.Ç., S.C., B.D., M.S., S.A., T.K.Y.; Data: M.Y., S.C.; Analysis: M.Y., T.K.Y.; Literature search: M.Y.; Writing: M.Y.; Critical revision: M.Y., T.Y., İ.S., C.Ç., S.C., B.D., M.S., S.A., T.K.Y.

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DENEYSSEL ÇALIŞMA - ÖZ

Hyaluronik asit ve kondroitin sülfat kombinasyonunun radyasyon proktiti oluşturulmuş sıçanlardaki etkinliği

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AMAÇ: Bu çalışma, akut radyasyon proktiti (ARP) sıçan modelinde hyaluronik asit ve kondroitin sülfat kombinasyonunun (HA/CS) profilaktik ve terapötik etkilerini araştırmak için tasarlandı.

GEREÇ VE YÖNTEM: Sıçanlar beş gruba ayrıldı: SHAM; radyasyon (IR) + salin (5. ve 10. gün boyunca 1 mL); IR + HA/CS (5. ve 10. gün boyunca 1 mL). Her sıçana 17.5 Gy'lik tek bir fraksiyon RT verildi. HA/CS, ışınlamadan sonra her gün rektal yoldan uygulandı. Her sıçan, proktit belirtileri açısından günlük olarak gözlemlendi. Mukozal değişiklikler makroskopik ve patolojik olarak değerlendirildi.

BULGULAR: Klinik bulgulara göre IR + salin grubundaki beş sıçan 10. günde 3-4 derece semptomlar izlendi. IR+ salin ve IR + HA/CS grupları arasında 5. günde makroskopik bulgu skorlarında anlamlı bir fark gözlemlenmedi. Patolojik incelemede, salinle tedavi edilen sıçanlarda ışınlamadan 10 gün sonra radyasyona bağlı mukozal hasar en belirgin bulguydu. IR + HA/CS 10. gün grubunda 1-2 derece patolojik bulgulara karşılık gelen hafif inflamasyon ve hafif kript değişiklikleri gösterdi.

TARTIŞMA: Radyasyon sistitinde kullanılan HA/CS, radyasyon proktitinde de faydalı olabileceği düşünülmektedir.

Anahtar sözcükler: Hyaluronik asit; kondroitin sülfat; radyasyon proktiti.

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