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Tranexamic Acid and Hyaluronate/Carboxymethylcellulose Create Cell Injury

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ABSTRACT

Background and Objectives: Postoperative pelvic adhesions are associated with chronic pelvic pain, dyspareunia, and infertility. The aim of this study was to evaluate the adhesion prevention effects of tranexamic acid (TA) and hyaluronate/carboxymethylcellulose (HA/CMC) barrier in the rat uterine horn models on the basis of macroscopic and microscopic adhesion scores and histopathological as well as biochemical parameters of inflammation.

Methods: Twenty-one Wistar rats were randomly divided into 3 groups. Ten lesions were created on the antimesenteric surface of both uterine horns by bipolar cautery. Three milliliters of 0.9% sodium chloride solution were administered in the control group. A single layer of 2 × 2 cm HA/CMC was plated in group 2. Two milliliters of TA was applied in the last group. All rats were sacrificed at postoperative day 21.

Results: No significant difference was found among the control group, the HA/CMC group, and the TA group in terms of macro-adhesion score ($P = .206$) and microadhesion score ($P = .056$). No significant difference was found among the 3 groups in terms of inflammation score ($P = .815$) and inflammatory cell activity ($P = .835$). Malondialdehyde levels were significantly lower in the control group than in the TA group and HA/CMC group ($P = .028$). Superoxide dismutase and glutathione S-transferase activities were found to be higher in the control group than in the TA group ($P = .005$) and HA/CMC group ($P = .009$).

Conclusions: TA and HA/CMC had no efficacy in preventing macroscopic or microscopic adhesion formation and decreasing inflammatory cell activity or inflammation score in our rat models. TA and HA/CMC increased the levels of free radicals and reduced the activities of superoxide dismutase and glutathione S-transferase enzymes, which act to reduce tissue injury.

Key Words: Adhesion, Hyaluronate/carboxymethylcellulose, Rat, Tranexamic acid, Uterine horn.

INTRODUCTION

Postoperative abdominal/pelvic peritoneal adhesions are a major source of morbidity (eg, bowel obstruction, infertility, ectopic gestation, as well as chronic pelvic pain) in women.[1] It has been indicated that exists presently no single universally accepted agent that would be used in routine practice to efficiently and cost-effectively prevent or at least reduce intraperitoneal adhesion formation or reformation.[2]

Basic mechanisms underlying the adhesion formation are thought to be inadequate tissue oxygenation that is regulated by locally released hormones and growth factors in normal conditions, and exaggerated leukocyte-dependent inflammatory response caused by free radicals and their metabolites.[3,4] Although hypofibrinolysis has been thought to be an important factor in postoperative adhesion formation, studies on fibrinolytic mediators have yielded controversial results.[5]

Tranexamic acid (TA) is a synthetic derivative of the amino acid lysine. TA is a potent antifibrinolytic agent commonly used in elective surgical procedures. TA use has routinely been shown to be successful in the treatment of abnormal uterine bleeding and postpartum bleeding.[6,7]

Sodium-hyaluronate/carboxymethylcellulose–based membranes are thought to act as a mechanical barrier and thereby prevent the formation of postsurgical adhesions.[8] Some animal and human studies have shown macroscopic reduction in the intensity of adhesions following abdominal and pelvic surgeries with the use of hyaluronate/carboxymethylcellulose (HA/CMC) barriers.[9,10]

The aim of this study was to evaluate adhesion prevention effects of TA and HA/CMC in the rat uterine horn models

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on the basis of macroscopic and microscopic adhesion scores and histopathological and biochemical parameters of inflammation.

METHODS

The study was launched after obtaining approval from the Experimental Animals Ethics Committee of Yeditepe University. All experiments and evaluations were completed between December 25 2012 and March 4 2013. The Helsinki Declaration was taken as the basis for the use of experimental animals. In accordance with the 3R (replacement-refinement-reduction) rule, we used the minimum number of rats necessary to achieve scientific objectives and produce statistically significant results. Twenty-one female Wistar albino rats, 10 to 14 weeks old, weighing 250 to 300 g, which were not previously analyzed in other studies, were used. All rats were kept under well-controlled environment in terms of temperature (21°C–24°C), humidity (40%–60%), and illumination (12 hours of light/12 hours of dark regimen) before and after the operation. The rats were fed ad libitum. All rats were monitored for their health status for 7 days before the operation. All rats were administered with ketamine 100 mg/kg (Ketalar; Eczacibasi, Istanbul, Turkey) and xylazin 10 mg/kg (Rompun; Bayer, Istanbul, Turkey) before the operation, and anesthesia was maintained for 20 to 60 minutes. Postoperative analgesia was achieved by parenteral injections of Petidin (Aldolan; Liba, Istanbul, Turkey). All operations were conducted by the same surgeon. Laparotomy was performed through a 3-cm abdominal midline incision. Ten uniform lesions were created at the bifurcation of uterine horns in a 2 × 2 cm area in each rat. The lesions were created on the antimesenteric surface by applying 10 W for 1 second with bipolar cautery.[11] Rats were randomly assigned to 3 equal groups, each consisting of 7 rats similar to previous models.[12,13] Before closure of the abdomen, rats in the control group were administered intraperitoneally with 3 mL of 0.9% sodium chloride solution.[14] In group 2, traumatized areas on the uterine horns were covered by a single layer of 2 × 2 cm HA/CMC films before closure. In group 3, 2 mL of TA was applied on the traumatized areas on the uterine horns using a sterile injector. The abdominal wall was then closed with 2/0 Vycril (polyglactin 910) interrupted sutures. The rats were followed during their recovery for 21 days. All rats were sacrificed at postoperative day 21.[11] The abdomen was opened through a transverse incision while carefully making the incision just above the previous laparotomy site. The peritoneal cavity and uterine horns were assessed **(Figure 1)**.

Figure 1. First step of the initial surgery and the adhesion formation detected at the second operation.

Macroscopic evaluation was conducted for intrapelvic adhesions and for the adhesions in the uterine horns. Macroscopic adhesion scoring was performed by the same surgeon in a double-blind fashion. An adhesion point-scoring system was used for macroscopic evaluation in which 0 = no adhesion; 1 = mild traction is required to detach the adhesion; 2 = moderate traction is required to detach the adhesions; 3 = sharp dissection is required to detach the adhesion.[15]

In the microscopic evaluation of intrapelvic adhesions, microscopic extent of the fibrosis was scored according to the point method by Hooker et al[16] in which 0 = no fibrosis; 1 = minimal, loose fibrosis; 2 = moderate fibrosis; and 3 = intense fibrosis by the same pathologist in a double-blind fashion.

Uterine horns were removed from sacrificed rats as a block together with the organs with which they formed adhesions and fixed in 10% formaldehyde for pathological examination (**Figure 2**). Paraffin-embedded tissue blocks

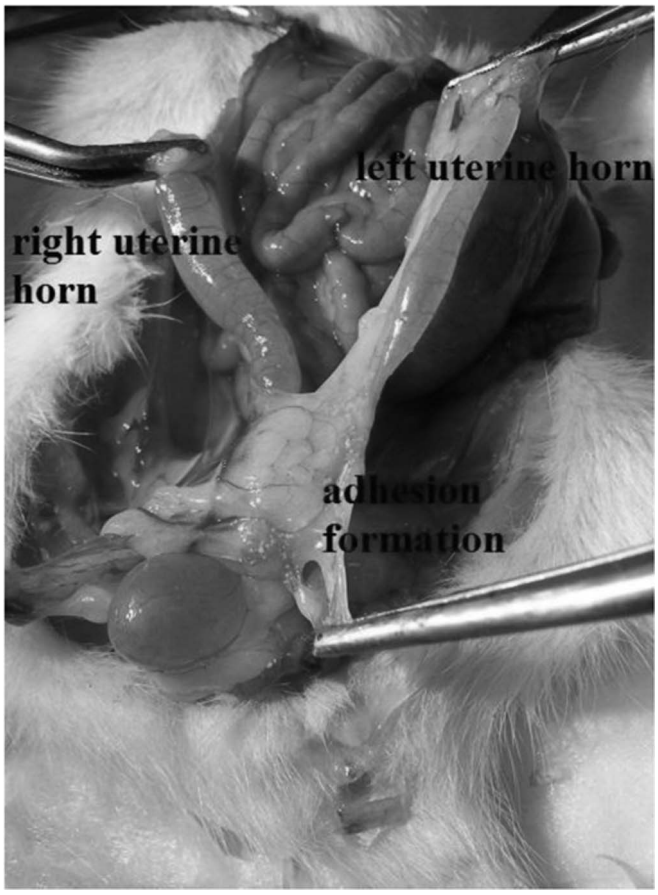

Figure 2. Malondialdehyde (MDA) levels and superoxide dismutase (SOD) and glutathione S-transferase (GST) activities in the control group, the tranexamic acid (TA) group, and the hyaluronate/carboxymethylcellulose (HA/CMC) group.

were prepared and paraffin blocks were sectioned to obtain 5-μm tissue sections and mounted on slides. Tissue sections were stained with hematoxylin and eosin and all samples were examined under light microscopy (at 100×, 200×, and 400× magnification) by the same pathologist in a double-blind fashion. The inflammation in the adhesion tissue was scored quantitatively on a point system in which 0 = no inflammation; 1 = the presence of giant cells, rare plasma cells, and lymphocytes; 2 = the presence of giant cells, plasma cells, eosinophils, and neutrophils; and 3 = abundant inflammatory cells and micro abscesses.[16] Activity of the inflammatory cells (leukocytes) within the adhesion tissue was calculated according to the modified scoring system by Philips et al.[17]

Adhesion sites in the uterine horns (around 0.40 g [minimum to maximum: 0.142–0.487 g]) were homogenized (IKA ultra turrax T 25 basic; IKA Labotechnik, Staufen, Germany) in ice-cold phosphate buffered saline ([ph 7.4]; 1:10 weight/volume [w/v]). The level of free radical tissue damage (malondialdehyde levels) and antioxidant enzyme activities (superoxide dismutase [SOD] and glutathione S-transferase [GST]) in the homogenates were examined. All procedures were performed at 4°C. The changes in malondialdehyde (MDA) levels were measured by the spectrophotometric method.[18] MDA is the end product of lipid peroxidation and reacts with thiobarbituric acid reactive substances to form a pink-colored product. This pink color was read in a spectrophotometer (Agilent 8453 UV-Visible spectroscopy system) at 532 nm. MDA levels were expressed in nmol/g.

SOD activity was determined based on inhibition of nitroblue tetrazolium (NBT) reduction in xanthine-xanthine oxidase system.[19] Superoxide radicals reduce NBT to form blue-colored formazan, which has an absorbance maximum at 560 nm. In the absence of the enzyme, the reduction of NBT produces a deep blue-purple color, whereas the presence of SOD inhibits the reduction of NBT. SOD activity was expressed in U/mg.

The measurement of GST activity was based on the conjugation of 1-chloro-2,4-dinitrobenzene with reduced glutathione, a reaction which is accompanied by an increase in absorbance that is read at 340 nm.[20] The method described by Lowry et al[21] was used to measure protein levels. GST activity was expressed in mol min 1 mg 1 protein.

Statistical Analyses

The Kruskal-Wallis test was used in the analysis of score data and quantitative data not showing normal distribution according to Shapiro-Wilk test results. For comparing groups, mean rank test was done following statistically significant Kruskal-Wallis results. PASW 18 and Statistica 8 statistical packages (formerly SPSS Statistics/IBM Corporation) were used in statistical analyses. P values < 0.05 were considered statistically significant. Data were summarized by median (minimum to maximum) as tables.

RESULTS

No significant difference was found among the control group, the HA/CMC group, and the TA group in terms of macroadhesion score ($P = .206$). Microadhesion score also did not significantly differ among the 3 groups ($P = .056$) **(Table 1)**.

No significant difference was found among the control group, the HA/CMC group, and the TA group in terms of

Table 1.
Comparison of the Control, TA, and HA/CMC Groups in Terms of Macroadhesion, Microadhesion, and Inflammation Scores and Inflammatory Cell Activity

	Control Group	TA Group	HA/CMC Group	*P* Value*
Macroadhesion score	3 (0–3)	2 (0–3)	1 (1–3)	.206
Microadhesion score	1 (1–2)	2 (1–3)	2 (1–3)	.056
Inflammation score	1 (1–2)	1 (1–2)	1 (1–2)	.815
Inflammatory cell activity	1 (1–3)	1 (1–3)	1 (1–3)	.835

Abbreviations: CMC, carboxymethylcellulose; HA, hyaluronate; TA, tranexamic acid.

*$P < .05$ was considered statistically significant.

inflammation score ($P = .815$) and inflammatory cell activity ($P = .835$) (Table 1).

MDA level ($P = .028$), SOD activity ($P = .005$), and GST activity ($P = .009$) were significantly different among the 3 groups **(Table 2).** According to multiple comparisons, MDA levels did not show statistically significant differences according to mean rank test, but there is a clinically meaningful difference among the control group and the other groups. MDA levels were lower in the control group compared with those in the TA group and the HA/CMC group. SOD and GST activities were found to be significantly higher in the control group than in the TA group and the HA/CMC group ($P < .05$). MDA levels, SOD, and GST activities did not significantly differ between the TA group and the HA/CMC group ($P > .05$) **(Table 2)**.

DISCUSSION

Peritoneal healing differs from that of other tissues. Epithelization occurs simultaneously in all injured sites of peritoneum. However, in other tissues, epithelization proceeds from the wound margins toward the center. Fibrin deposits of the traumatized peritoneum are dissolved through fibrinolytic activity and enter systemic circulation.[22] Persistent fibrin deposits enhance pathways of adhesion. Substances locally released by fibroblasts, mesothelial, and immune cells in the traumatized epithelium stimulate remodeling, angiogenesis, and formation of extracellular matrix, which forms the core structure of adhesions.[23]

TA, a competitive inhibitor of plasmin and plasminogen, is a hemostatic agent and is orally, locally, or parenterally administered in surgical procedures or to treat abnormal uterine bleeding and postpartum hemorrhage.[6,7] Increased plasmin activity and/or D-dimer levels have been shown to trigger the release of proinflammatory cytokines such as interleukin 6 and increase the number of inflammatory mononuclear cells.[24] TA decreases plasmin, D-dimer levels, and inflammatory response. In the present study, the anti-inflammatory activity of TA by blocking plasmin activity and/or D-dimer levels was expected to reduce the adhesion formation. However, we found no significant difference compared with the control group in terms of macroadhesion score and microadhesion score. Wiseman et al[25] reported reduction in adhesions using TA in fibrin formulations in rat peritoneal adhesion model. In vivo TA has been suggested to suppress the migration of inflammatory cells and postischemic exaggerated neutrophilic response in ischemia/reperfusion injury in rats.[26] In our study, however, inflammation score and inflammatory cell activity in the TA group were not significantly different than those in the control group.

MDA, an end product of the lipid peroxidation, is a free radical released by the breakdown of unsaturated fatty acids found in the cell membranes.[2] MDA levels decrease with the increasing antioxidant enzyme activities. GST and SOD activity levels are the indicators of antioxidant enzyme activity against oxidative stress. GST is a phase II detoxification enzyme that protects cells against chemical toxicity and ox-

Table 2.
Comparison of the Control, TA, and HA/CMC Groups in Terms of MDA Level and SOD and GST Activity

	Control Group	TA Group	HA/CMC Group	*P* Value*
MDA level, nmol/g	1.834 (0.389–2.156)	2.933 (1.478–6.293)	2.197 (1.986–4.399)	.028*
SOD activity, U/mg	2.338 (2.158–3.684)	0.566 (0.019–0.802)	0.638 (0.466–0.987)	.005*
GST activity, μmolmin^{-1} mg^{-1} protein	3.457 (1.713–8.568)	0.553 (0.084–2.756)	0.945 (0.613–1.956)	.009*

Abbreviations: GST, glutathione S-transferase; MDA, malondialdehyde; SOD, superoxide dismutase; other abbreviations as in Table 1.

*$P < .05$ was considered statistically significant.

GST, glutathione S-transferase (mol min 1 mg 1); MDA, malondialdehyde (mol/g); SOD, superoxide dismutase (U/mg).

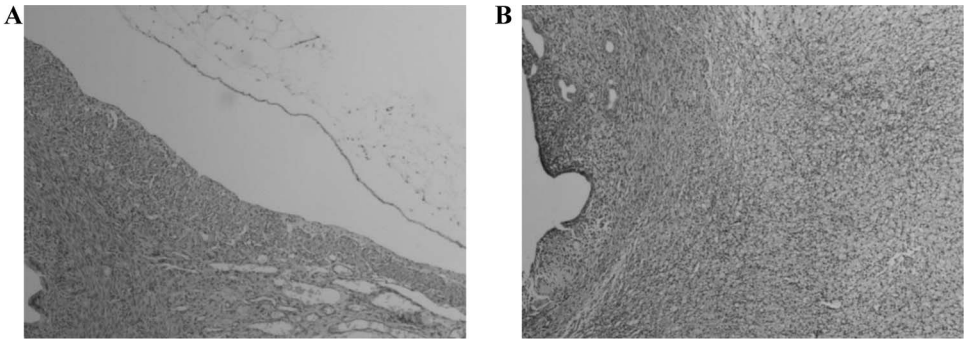

Figure 3. There was no adhesion in a rat uterine horn administered intraperitoneally with 3 mL of saline **(A).** There was chronic active inflammation with severe lesions, histiocytic proliferation, and fibrosis in a rat uterine horn covered by a single layer of HA/CMC film **(B).** (Hematoxylin and eosin 100×).

idative stress by reducing glutathione. SOD is a basic cellular defense mechanism against free radicals such as MDA.[27] Reduced SOD and GST activities are associated with increased production of free radicals. Increased levels of free radicals and lipid peroxidation result in an increase in vascular permeability and serosanguinous exudation that trigger adhesion formation. In our study, MDA levels were higher in the TA group. SOD activity and GST activity were found to be lower in the TA-treated group compared with those in the saline-treated control group. According to our study, TA may have a potential role in creating tissue injury, and thus, adhesion formation.

In our study, macroscopic and microscopic adhesion scores did not differ significantly between the HA/CMC group and the control group. Also, inflammation score and inflammatory cell activity were not significantly different between the HA/CMC group and the control group. In the present day, HA/CMC is commonly used in gynecological procedures. Controversial results exist regarding macroscopic and microscopic adhesion preventive effects of HA/CMC.[9,10,28,29] It has been suggested by Vetere et al[28] that there is a borderline difference between HA/CMC and the saline-treated rats in terms of histopathological parameters of inflammation in rat uterine horn model. De Laco et al[29] claimed that HA/CMC has histopathologically and clinically reduced adhesions. The US Food and Drug Administration revoked the license of substances containing carboxymethylcellulose and hyaluronic acid due to lack of efficacy in human studies.[30]

HA/CMC might react with the large area of the injured peritoneum and induce a strong inflammatory response. HA/CMC-related complications were most commonly observed in patients who underwent gynecologic debulking surgery. HA/CMC-associated sterile peritonitis and acute inflammation following administration has been reported in patients who underwent bilateral salpingo-oophorectomy, cesarean delivery, and total hysterectomy.[31,32] Our results suggest that HA/CMC reduces the activities of SOD and GST in tissues. MDA levels were also higher in HA/CMC applied tissues. HA/CMC reduced the levels of basic cellular protective enzymes and increased free radicals in our study. Probably it is associated with the persistence of inflammatory response in the form of uncontrolled active or chronic-active inflammation **(Figure 3).**

TA is widely administered to treat abnormal uterine bleeding and postpartum hemorrhage locally or parenterally; however, in our rat uterine horn model, we showed no efficacy in preventing adhesion formation. TA may block activities of SOD and GST enzymes, which are cell protective enzymes. Administration of HA/CMC did not prevent adhesion formation in this study. The finding that HA/CMC reduced the activity of SOD/GST enzymes suggests that safe use of HA/CMC is debatable.

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