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The Antiadhesive Effects of Bemiparin Sodium vs Hyaluronic Acid on a Rat Uterine Horn Adhesion Model: A Randomized Controlled Experimental Study

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Abstract

Introduction: To determine the antiadhesive effects of bemiparine sodium compared to hyaluronic acid based jel on a standard adhesion formation model of rat uterine horn.

Materials and Methods: Twenty non-pregnant female Sprague Dawley rats weighing 180-220 g were used to inflict a standardized model of adhesion formation on a rat uterine horn. The rats were randomized into four groups. Control group (group 1), bemiparin group (group 2), HA (hyaluronic acid) group (group 3) and bemiparin+hyaluronic acid group (group 4). Each group consisted of 5 animals. In all groups, ten standardized lesions were inflicted on the right uterine horn using bipolar cauterization with 10 watt power. The uterine horns of 20 rats were evaluated macroscopically, microscopically and with immunohistochemistry. For macroscopic evaluation; "adhesion type", "adhesion tenacity", "extent of adhesions" and "total macroscopic adhesion score" were determined. For microscopic evaluation; inflammation and fibrosis formation was evaluated. Immunohistochemistry scoring was performed utilizing VEGF (Vascular Endothelial Growth Factor) and TGF-β1 (Transformic Growth Factor beta-1) markers.

Results: Macroscopic adhesion scores, including "adhesion type", "adhesion extent" and "total macroscopic adhesion score" in the bemiparin+HA group (group4) was significantly lower than those in the control group (group1) and group HA (group3) ($p<0.05$). Among these three categories;bemiparin +HA (group4) had a significantly lower score than group HA (group3) in terms of adhesion type ($p<0,01$) and bemiparin group (group2) had a lower score than HA group (group3) in in terms of adhesion extent ($p<0,05$). There were no statistical differences across all four groups for microscopic inflammation, fibrosis and immunohistochemistry staining.

Conclusion: The combined use of bemiparin and HA may be effective in preventing macroscopic pelvic adhesion formation. Clinical trials on humans should be conducted for further recommendations.

Keywords: Adhesion**;** pelvic adhesion; bemiparin; hyaluronic acid; VEGF; TGF-β1

Introduction

Pelvic adhesions are abnormally located fibrous connections between tissues and they are mostly formed after surgical procedures. They may also occur after ischemia, endometriosis, infection or foreign body reactions (1). Pelvic adhesions are one of the major causes of infertility, bowel obstructions, chronic pelvic pain and repetitive surgical operations (2). Disruption of adnexal anatomy by adhesions prevents gamete and embryo transport and effect fertility adversely (3). Furthermore pelvic adhesions may be responsible for bowel obstructions along with chronic pelvic pain by imparing organ motility (4). There is also a financial aspect to "adhesion related medical complications" since the expenditures of adhesiolysis patients exceed 2.5 billion dollars annualy worlwide (5). Although adhesion patophysiology has not been distinctly elucidated

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we have gathered from cumulative literature that multifactorial contributing factors play role in adhesion formation. In simplicity; adhesion formation prerequisites include: inflammatory response, fibrinogen accumulation, dysregulated balance of fibrogenesis and angiogenesis (6). The most promising group of agents to be evaluated in terms of preventing formation of surgically induced adhesions are barrier agents (7,8). Barriers can be found in the form of membranes or gels. They are effective in separating injured and/or damaged peritoneal surfaces. Barrier agents' raw material can be either; oxygenated regenerated cellulose, polytetrafluoroethylene or hyaluronan-based agents. The collective results of studies conducted in humans and animals, demonstrate that the use of hyaluronan based agents have shown an inhibitory effect on adhesion (9). Studies also have been conducted with anticoagulants, especially with low molecular weight heparin, demonstrating the reduction of the formation of intra-abdominal adhesions by affecting the coagulation cascade. Enoxaparine is the most widely used agent in adhesion models (10,11). Heparin increases the degradation of thrombin by preventing the formation of thrombin and forming a complex with antithrombin III. Factor Xa is also inhibited by heparin which enhances the plasminogen activator activity and causes an increase in the activation of plasminogen. Bemiparin; another low molecular weight heparin, is also a Factor Xa inhibitor. Fibrin deposition, which is the second phase of adhesion formation is decreased with factor Xa inhibitors. Thus the end result is a decline in adhesion formation. In this experimental animal study, our objective was to investigate the preventive effects of bemiparin Na versus hyaluronic acid gel in pelvic adhesion formation on a rat uterine horn model. The primary outcome of the study was the reduction in the size of the macroscopic pelvic adhesions. The secondary outcomes were "change in microscopic histological scores" and "immunohistochemical evaluation with VEGF (Vascular Endothelial Growth Factor) and TGF-β1 (Transformic Growth Factor beta-1); as markers of "angiogenesis" and fibrosis".

Materials and Methods

Animals: Twenty non-pregnant female Sprague Dawley rats weighing 180-220 g were included in the study to perform a previously validated model of postoperative adhesion formation. The animals were fed in cages in accordance with the international ethical standards, kept at the appropriate temperature and 12-hour day and night cycles were provided.

Surgical procedures: Adequate sedation was provided with 10 % ketamine preoperatively. The surgical site was cleaned with 10 % povidone iodine solution. A 4 cm mid-vertical line incision was made. Right uterine horn was detected and 10 standard lesions were created with 10 watt cautery (Valleylab™ FT10). All surgical procedures were performed in sterile circumstances by the principal researchers (SB and AFGK). Following completion of standard lesions animals were randomized to control (Group 1), bemiparin Na (Group 2), hyaluronic acid gel (Group 3) and the combined use of these two agents (Group 4) according to a randomization protocol employed by the veterinarian. In the control group (n=5) 1ml SF (sérum physiologique) was injected intraperitoneally; in the second group (n=5) 700U bemiparin Na (Hibor©, Dem İlac,Turkey) was applied around the uterine horn intraperitoneally; in the third group (n=5) 0,5 ml hyaluronic acid based barrier gel (Betamix©, Betatech Medical,Turkey) was applied evenly over the uterine horn; in the fourth group (n=5) bemiparin Na and hyaluronic acid based gel were applied concomitantly. After hemostasis was achieved, the surgical site was washed with 2 ml of saline before abdominal closure. The abdominal incision was closed in two layers: the musculo-peritonoeal layer and fascia were closed with 4/0 polyglycolic acid (Vicryl, Ethicon Inc) in simple interrupted sutures and the skin was closed with 3/0 polyglycolic acid (Vicryl, Ethicon Inc) in the same manner.

Postoperative care: Upon completion of anesthetic recovery, rats were housed separately under optimum conditions; 12 hour light and 12 hour dark cycle, 40-60% humidity and 21-24°C temperature was controlled by the research facility. Sufficient oral analgesia was provided for postoperative 2 days and surgical incisions were checked daily to avoid surgical site infections. Animals were housed in suitable conditions until the 14th postoperative day and were visited daily by the primary researcher SB. Their physical activity, feeding patterns and postsurgical wound sites were controlled by SB on daily visits. On the 14th postoperative day, the animals were sacrificed with high dose ether anesthesia. The abdomen was entered with a U-shaped incision and the uterine horns were evaluated macroscopically. Following the macroscopic evaluation, the tissues with adhesions were excised and transferred to the pathology department after being placed in 10 % formalin solutions. The results were evaluated in three categories;

Table 1: Adhesion extent,type and tenacity scoring system for macroscopic evaluation

1.Score	Adhesion extent	Adhesion type	Adhesion tenacity
0	No uterine adhesion	No adhesions	No adhesions
1	1-25% involvement	Filmy avascular adhesions	The adhesion can be seperated from tissue with gentle traction
2	26-50% involvement	Vascular or opaque adhesions	The adhesion can be seperated from tissue with moderate traction
3	51-75% involvement	Cohesive attachment of the uterine horn to the abdominal side	Adhesion requiring sharp dissection
4	76-100% involvement		

Table 2: Adhesion scoring system for microscopic evaluation

Score	Fibrosis	Inflammation
0	None	None
1	Minimal, loose	Giant cells, lymphocytes, plasma cells
2	Moderate	Giant cells, eosinophils, neutrophils
3	Florid, dense	Many inflammatory cells, microabscess

1.Macroscopic examination: Two weeks after standard lesions were applied to the uterine horns, rats were anesthetized and the abdomen was reached utilizing U shaped incisions. The rats whose groups were known by the veterinarian in the Bezmialem Vakif University Experimental Animal Laboratory were numbered with "tail markers" from 1 to 20 randomly. Macroscopic scoring was done by two researchers who were blinded to the "tail mark". Adhesions were evaluated according to previous scoring systems which have been clinically defined and validated (12). The extent of adhesion was designated as follows (Table 1) 0= no adhesion, 1= 1-25% of the surface covered, 2= 26-50% of the surface covered, 3= 51-75% of the surface covered and 4= 76-100% of the surface covered. Adhesion type was designated as follows (Table 1) 0= no adhesions, 1= filmy avascular adhesions, 2= vascular or opaque adhesions, 3= cohesive attachment of the uterine horn to the abdominal site. Adhesion tenacity was designated as follows(Table 1) 0= no adhesions 1= if the adhesion seperated from tissue with gentle traction 2= if adhesions seperated from tissue with moderate traction 3= requiring sharp dissection. The "total macroscopic adhesion score" was obtained by summarizing these three different scores.

2.Microscopic evaluation: After macroscopic evaluation, all tissues which included adhesion formation were excised and the tissue specimens were fixed in a 10 % neutral buffered formaldehyde solution. Following the dehydration procedure, all samples were embedded in paraffin. Three micrometer thick sections were cut by a microtome. Subsequent to deparaffinization, the samples were stained with hematoxylin and eosin (HE). The slides were inspected under a light microscope by a pathologist (NS) who participated in the study and was blinded to the treatment groups. The level of inflammation was scored as follows (Table 2): 0 = no inflammation, 1 = giant cells, occasional lymphocytes, and plasma cells, 2 = giant cells, eosinophils, and neutrophils, and 3 = presence of many inflammatory cells and microabscesses. The degree of fibrosis was graded as follows: 0 = no fibrosis, 1 = minimal, loose, 2 = moderate, and 3 = dense.

3.Immunohistochemical analysis: All immunehistochemical analysis were performed by NS and ST. Scoring was perfomed as demonstrated in Table 3.

a.VEGF staining: Four micrometer thick sections of formalin-fixed paraffin embedded tissues were placed on 3-aminopropyletxylene-covered slides. Subsequently, they were stained

Table 3: Immunohistochemistry scoring system

Score	VEGF, TGF-β1 staining
0	No staining
1	Weak, <33% positive staining
2	Moderate, 33-66% staining
3	Strong, >66% staining

TGF-β1: Transforming growth factor beta1; **VEGF:** Vascular endothelial growth factor.

with mouse monoclonal VEGF antibody (1/100titer; clone VG-1 sc-53462 Mouse monoclonal antibody) following the manufacturer`s protocol. Staining was performed on the Ventana BenchMark Ultra (Ventana Medical Systems Inc.). The staining protocol included Cell Conditioning 1 for 64 min, pre-peroxidase inhibition and primary antibody incubation for 1 hour and 20 min at 37 C. DAB IHC Detection Kit (Ventana Medical Systems) was used to detect VEGF protein expression. Tissues were counterstained with Hematoxylin for 16 min and Bluing Reagent for 4 min.

b.TGF-β1 staining: Four micrometer-thick sections of formalin-fixed paraffin embedded tissues were placed on 3-aminopropyletxylene-covered slides. Subsequently, they were stained with mouse monoclonal TGF-β1 antibody (1/100 titer; clone TB21 sc-52893 Mouse monoclonal antibody) following the manufacturer`s protocol. Staining was performed on the Ventana BenchMark Ultra (Ventana Medical Systems Inc.). The staining protocol included Cell Conditioning 1 for 64 min, pre-peroxidase inhibition and primary antibody incubation for 1 hour and 20 min at 37 C. DAB IHC Detection Kit (Ventana Medical Systems) was used to detect TGF-β1 protein expression. Tissues were counterstained with Hematoxylin for 16 min and Bluing Reagent for 4 min (13).

Ethical approval: This study was approved by the ethical committee of the Bezmialem Vakif University Experimental Animal Laboratory (219/2021). It was financially supported by a grant from the Bezmialem Vakif University (BVU:20210601E, 2022). The principal researchers (SB and AFGK) hold a certificate of ethical conduct of animal experimental research

Statistical analysis: Sample size determination: Power analysis for sample size was performed considering "adhesion extent" parameter. Based on a previous study (14) the difference between the means was 2.43 units, the standard deviation was 1.11. With 95% confidence level, pertaining an $\alpha = 0.05$ significance level for 80% power, the sample size was determined as n1=n2=n3=n4=5 with a total of "20" rats. The results were analyzed with the Shapiro-Wilk test. Kruskal Wallis test was used when the distribution of data was normal in comparisons of three or more groups. Dunn test was used for post-hoc comparisons of variables that were significant after Kruskal Wallis test. The descriptive statistics of the data are expressed as median (min-max). All statistical analyzes were analyzed in IBM SPSS version 26.0 (SPSS, Inc., Chicago, IL) at $p<0.05$ significance level.

Results

All rats tolerated the surgical procedures well and there were no mortalities. Each group was evaluated macroscopically in terms of "adhesion extent", "adhesion type", "adhesion tenacity" and "total macroscopic adhesion score" by two researchers in a double-blind manner (Table 4).(Figure 1).

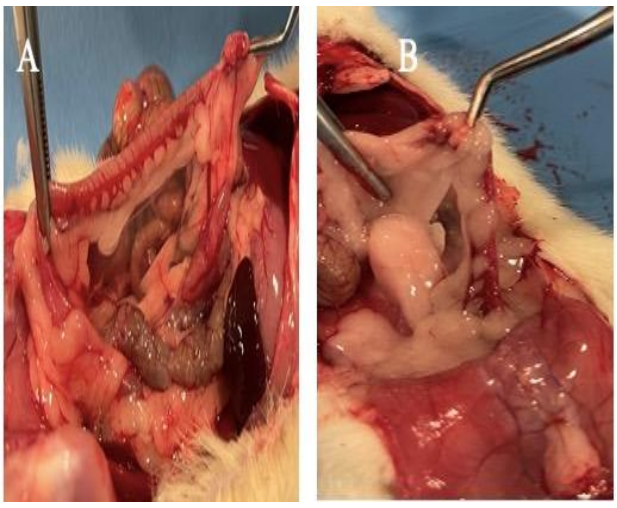

Figure 1 Caption: Macroscopic evaluation of adhesion formation by exposing the abdomen with a U-shaped incision after two weeks of standard lesions were applied to the uterine horns. a: no adhesion on uterine horn, b: 51-75% involvement, vascular/ opaque adhesions, separated from tissue with moderate traction.

There were statistically significant differences between four groups in terms of adhesion type, tenacity, extent and total scores ($p<0.05$). However there were no statistically significant differences in terms of microscopic scoring or immunohistochemical parameters (Table 4). When we employed post-hoc Dunn test we found that; macroscopic adhesion scores, including adhesion extent, type and total scores in Bemiparin Na+HA group (Group 4) were significantly lower than those in the control group (Group 1) ($p<0.05$) and group HA ($p<0.05$) (Table 5). Among these three categories of scoring, group Bemiparin Na+HA had a significantly lower score than group HA in adhesion type ($p<0.01$) and group Bemiparin Na had a slightly lower score than group HA in adhesion extent ($p<0.05$). There were no statistical differences across all four groups in the microscopic inflammation, fibrosis, and VEGF and TGF-β1 staining (Figure 2).

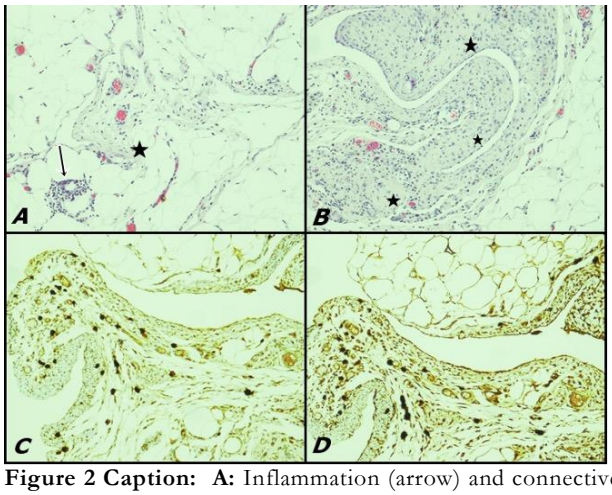

Figure 2 Caption: **A:** Inflammation (arrow) and connective tissue development (star) in adipose tissue (H&Ex100).**B:** Diffuse connective tissue and fibrosis development in adipose tissue (stars) (H&Ex100). **C:** Immunohistochemical TGF-B staining in connective tissue (IHCx100). **D:** Significant VEGF immunohistochemical staining in vascular structures (IHCx100)

Table 4: Comparison of macroscopic, microscopic, and immunohistochemistry scores

	Group 1 (n=5)	Group 2 (n=5)	Group 3 (n=5)	Group 4 (n=5)	P value
Macroscopic score					
Adhesion Type	2(1-3)	1(0-2)	2(1-3)	0(0-1)	0.035
Adhesion Tenacity	2(1-3)	0(0-3)	2(2-3)	0(0-2)	0.05
Adhesion Extent	3(1-4)	0(0-2)	3(1-3)	0(0-2)	0.032
Total Adhesion Score	7(3-7)	1(0-7)	8(4-8)	0(0-5)	0.027
Microscopic score					
Fibrosis	0(0-2)	1(0-1)	1(1-2)	1(0-2)	0.128
Inflammation	1(0-2)	1(1-2)	2(1-2)	1(1-2)	0.497
Immunohistochemistry					
VEGF	1(0-2)	1(1-2)	2(1-2)	2(1-2)	0.249
TGF-Beta1	1(0-1)	1(1-2)	1(1-2)	1(1-2)	0.132

CO: Control, **BNa:** Bemiparin **Na, HA:** Hyaluronic acid, **TGF beta1:** Transforming growth factor beta1, **VEGF:** vascular endothelial growth factor. Values are median (min-max). *****Kruskal Wallis test employed

Table 5: Post-hoc comparisons of macroscopic adhesion scores and microscopic fibrosis scores

	Group CO/Group BNa	Group CO/Group HA	Group CO/Group BNa+HA	Group BNa/Group HA	Group BNa/Group BNa HA	Group HA/Group BNa+HA
Type	0.219	0.717	0.024	0.111	0.301	0.009
Extent	0.051	0.956	0.03	0.045	0.826	0.026
Total	0.104	0.766	0.025	0.055	0.533	0.011

CO: Control, **BNa:** Bemiparin Na, **HA:** Hyaluronic acid *****Post-hoc Dunn Test employed

Discussion

The major findings of our study were that the "macroscopic adhesion scores", including "adhesion type", "adhesion extent" and "total adhesion scores" in the bemiparin Na+HA group (group4) were significantly lower than those in the control group (group1) and HA group (group3) ($p<0.05$).This finding, if backed by following studies; supports the possible utilization of bemiparin along with hyaluronic acid for adhesion prevention. It has been recognised that three biological processes play a role in the formation of adhesion: coagulation cascade, fibrin degradation

and inflammatory process (15). Traumas that trigger adhesion formation effect the peritoneum and lead to an inflammatory response, correspondingly; inflammation leads to the activation of fibrocoagulative pathways and formation of an exudate rich fibrin begins (16). If fibrin destruction can not occur through plasminogen and plasmin cascade, fibrous structures turn into collagen deposits. The first 5-7 days after injury is the ideal time for fibrin destruction to be completed (17). During this time, the fibrinolysis system can break down fibrinogen and fibrin. Elimination of fibrin depends on activation of plasminogen activator secreted from mesothelial cells located in the peritoneum, but in the presence of traumas, ischemia and/or inflammation this activation process is inhibited (18). Approaches used to reduce or eliminate adhesion formation involve "direct interference" with the above mentioned three mechanisms. Barrier agents containing HA were used to seperate damaged peritoneum from contacted organs in order for the healing process to work physiologically without advancing towards adhesion formation (19). HA derivatives also work to prevent adhesions by reducing fibrin formation and promoting the production of peritoneal mesothelial cells (17). Likewise we chose to compare HA; which is a well established anti-adhesive molecule with bemiparin which is a LMWH (Low Molecular Weight Heparin). There are several forms of LMWH available for clinical practice. Nadroparin, enoxaparin, tinzaparin, and bemiparin are some of these forms. Most studies have focused on enoxaparine's antiadhesive effects; other LMWH have been neglected. Bemiparin's antiadhesive features have not been studied prior to our experimental study. The main characteristics of this LMWH are its low anti-factor IIa (thrombin) anti-Xa activity and its skill in increasing the release and activity of tissue factor pathway inhibitor from endothelial cells (20). Although bemiparin's anti-adhesive properties have not been investigated prior to our experimental study ; it's antithrombotic and anti-angiogenic properties have been studied . Bemiparin reduced intimal hyperplasia and prevented thrombosis angiogenesis in a recent rat carotid artery reanastomosis model (21). Bemiparin has also gained popularity in the clinical setting for being a safe alternative to enoxaparine especially when tromboprophylaxis is desired (22,23). Furthermore LMWH have , been reported as antimetastatic agents through influencing cell adhesion molecules (24). In a recent clinical trial bemiparin proved a non-inferior efficacy compared to enoxaparin with a significant reduction in adverse events per 100 patients treated (25). Although "prevention of tumor metastasis" and "thromboembolism" may seem beyond the scope of this study; the biological processes underlying "adhesion formation" and " thromboembolism" formation are very similar and rely on the coagulation cascade (26). It is evident that bemiparin should be studied in the context of inhibiting cytokines and other adhesion molecules in following studies.

Study limitations: Furthermore we initiated a study to investigate a "molecule's antiadhesive properties which has not been documented before. The limitations we have faced are the experimental animal design; in vivo human conditions may alter the characteristics we studied. The major limitation of the study is that it is an experimental animal study. As per nature of animal studies; the results can not be directly extrapolated to human in vivo conditions.

Conclusion

According to our results; the combined use of bemiparin and HA is effective in preventing pelvic adhesion formation by macroscopic evaluation. However there is no significant differences between groups in terms of immunohistochemistry and microscopic evaluation. Further studies are still needed to evaluate the effectiveness of several prevention strategies for postoperative pelvic adhesions.

Data availability: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Ethical approval: : All animal treatment procedures were in accordance to the Principles of the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Bezmialem Foundation University. This study was approved by the ethical committee of the Bezmialem Vakif University University Experimental Animal Laboratory (219/2021).

Conflict of interest: The authors declare no competing interests.

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Author contribution: S.B and A.F.G.K performed the experiments and analyzed the data; N.S, S.T. performed the pathological and immunohisctochemical analyses; A.Y.T interpreted the results of the experiments; C.C; S. B., N.S., and G.İ. contributed to the discussion;

A.F.G.K and S. B. designed the research and wrote the manuscript.

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