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Platelet-rich Plasma Gel versus Hyaluronic Acid on Prevention of Peritoneal Abdominal Adhesion Formation in Rats

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Rezumat

Gelul cu plasmă bogată în trombocite versus acidul hialuronic pentru prevenirea formării aderențelor peritoneale la șobolani

Context: Formarea aderențelor intra-abdominale este încă inevitabilă şi reprezintă o cauză semnificativă de morbiditate în chirurgia abdominală. Gelul cu plasmă bogată în trombocite (PBT) şi acidul hialuronic au fost studiate pentru efectul lor protectiv împotriva formării aderențelor. Scopul acestui studiu a fost de a compara plasma bogată în trombocite şi acidul hialuronic în prevenirea aderențelor.

Material şi Metodă: Douăzeci şi şapte de şobolani Sprague-Dawley au fost împărțiți aleatoriu în trei grupuri egale (n=9). Trauma chirurgicală a fost utilizată pentru a induce formarea de aderențe. După intervenția chirurgicală, 1 ml de soluție ser fiziologic a fost instilat în cavitatea peritoneală în grupul de control (n = 9), 1 ml de acid hialuronic lichid (25 mg/ml) a fost instilat în grupul A (n = 9) şi 1 ml de plasmă bogată în trombocite a fost instilat în grupul B (n = 9). La patru săptămâni după intervenția chirurgicală inițială, a fost efectuată o laparotomie exploratorie şi aderențele au fost examinate microscopic şi macroscopic.

Rezultate: Gelul cu plasmă bogată în trombocite şi acidul hialuronic reduc macroscopic extensia şi gradul aderențelor. PBT se dovedeşte a fi superioară în reducerea rezistenței şi extensiei zonelor de aderență. Mai mult, PBT ameliorează formarea aderențelor abdominale prin reducerea neutrofilelor, a fibrozei şi a inflamației.

Concluzie: Rezultatele indică faptul că gelul cu plasmă bogată în trombocite este mai eficient decât acidul hialuronic în prevenirea aderențelor abdominale.

Cuvinte cheie: acid hialuronic (AH), plasmă bogată în trombocite (PBT), model intestinal de şobolan, aderențe abdominale, chirurgie experimentală

Abstract

Background: Intra-abdominal adhesion formation is still unavoidable and a cause of significant morbidity in abdominal surgery. Platelet-rich plasma gel and hyaluronic acid have been studied for their protective of therapeutic effects on adhesions. The aim of the present study is to compare Platelet-rich plasma and hyaluronic acid in adhesion prevention.

Material and method: Twenty-seven Sprague-Dawley rats were randomly allocated into three equal groups(n=9). Surgical trauma was used to induce adhesion formation. After trauma, 1 ml normal saline was instilled in the peritoneal cavity in control group (n=9), 1 ml liquid Hyaluronic acid (25 mg/ml) was instilled in group A (n= 9) and 1 ml of platelet-rich plasma was instilled in group B (n = 9). Four weeks after the laparotomy, a repetitive laparotomy was performed and adhesions were examined microscopically and macroscopically.

Results: Platelet-rich plasma gel and hyaluronic acid both reduce the extent and grade of adhesions macroscopically. Interestingly, PRP turns out to be superior in the reduction of tenacity and adhesion area. Moreover, platelet-rich plasma ameliorates abdominal adhesion formation by reducing neutrophils, fibrosis, and inflammation.

Conclusion: The results indicate that platelet-rich plasma gel surpasses hyaluronic acid in abdominal adhesion prevention.

Key words: hyaluronic acid (HA), platelet-rich plasma (PRP), rat intestinal model, abdominal adhesions, experimental surgery

Introduction

Peritoneal adhesions are abnormal fibrotic bands with an incidence up to 60-93% after abdominal and peritoneal operations associated with significant morbidity (1). Intra-abdominal adhesions appear to correlate with female infertility, pelvic pain, interstitial obstruction and increased post operative cost (2,3). A number of preventive strategies to reduce post-operative adhesions, such as administration of fibrinolytic products, antibiotic agents, anti-inflammatory drugs, nanofibrous membranes and solid barriers, have been used to prevent the formation of peritoneal adhesions after abdominal surgery (4,5). These current concepts of management include minimizing peritoneal trauma, preventing fibrin formation and employing physical barriers (6). A more detailed understanding of the pathogenesis on cellular and molecular level would aid the development of more effective preventive treatments.

During intra-abdominal operations, inflammatory cells increase the secretion of cytokines resulting in the migration of inflammatory cells and fibroblast to the injured peritoneum (7). Profibrotic transforming growth factor β (TGF-β) in the peritoneal cavity is released by activated fibroblast and mesothelial cells (8). Identifying suitable agents for preventing post-surgical intra-abdominal adhesion formation remains an important clinical challenge. Experimental studies have demonstrated reduction in peritoneal adhesions by influencing the intrabdominal metabolism after trauma with the use of medications such as free radical

scavengers and certain growth factors.

Hyaluronic acid is a glycosaminoglycan, naturally occurring from extracellular matrix components. Under aqueous physiological conditions, hyaluronic acid forms a highly viscous solution that appears to coat serosal surface. This quality offers a degree of protection against serosal desiccation. Hyaluronic acid can provide physical support and mechanical protection, which is thought to reduce the incidence of adhesions by regulating the inflammatory response and promoting vascular regeneration and wound healing (9). Clinical studies show that the release of protease is inhibited by peritoneal leukocytes and, correspondingly, the release of oxygen radicals is inhibited by macrophages. Furthermore, free oxygen radicals are scavenged. Other studies suggest that hyaluronic acid gel reduces the number of organs involved in adhesion formation in an ischemic button model (10). Moreover, experimental studies report to lower that the plasminogen inhibitor activity, reducing postoperative adhesions is lowered (11).

Platelet-rich plasma gel is an autologous concentration of platelets structurally similar to the fibrin clot (12). PRP involves modulation of the endo-abdominal environment by introducing various growth factors products, such as platelet-derived growth factor AB (PDGF-AB), transforming growth factor b-1 (TGFb-1) and vascular endothelial growth factor (VEGF), and, thus, recruits repairing cells to the site of tissue damage, which are essential to natural wound healing and leads to reduced inflammatory distress (13). Interestingly, the local use of platelet rich plasma gel has been proven to aid the healing of colonic anastomosis in rat models (14).

In the present day, there are insufficient data comparing the antioxidative and anti-inflammatory properties of Hyaluronic acid and Platelet-rich plasma gel in an abdominal adhesion in an animal model.

Materials and Methods

Animal experimentation was performed in the Laboratory for Experimental Surgery and Surgical Research "N.S. Christeas" (Athens, Attica, Greece) and the protocol was evaluated and approved by the Veterinary Service of the Prefecture of Athens (ref. no. 5175-June 2007) in compliance with Greek legislation (presidential. decree. 160/91) and European Community regulations (directive 309 of 1986 license according to E.U. legislation). Experiments were performed according to the Presidential Decree 56/2013 which harmonizes Greek legislation with the European Community Directive 63/2010 on the Protection of Animals Used for Scientific Purposes. Twenty-seven male Sprague Dawley rats (Rattus norvegicus domestica) weighing 350-450 g were enrolled in this experiment. Prior to the surgery the animals were kept in comfortable cages at 22 to 25 degrees of Celsius with free access to food and tap water for 1-week acclimation period under strict sanitary conditions.

Rats were randomly distributed into the following three groups:

- Control group (n=9): 1 ml normal saline was instilled in the peritoneal cavity.
- Group A (n=9): Hyaluronic group (1 ml of hyaluronic acid was instilled intraperitoneally around the lesion surface. In particular, HA gel was used, namely Hyamira Forte, product by Implant Industry Hellas A.E. with a concentration of 25 mg/ml).
- Group B (n =9): Platelet-rich plasma gel group (intraperitoneal PRP in the form of gel at a similar dose to Hyaluronic acid).

After adequate shaving and anaesthesia of the animal, the skin was sterilized with iodine povidone in a 10% solution. We entered the peritoneal cavity with a median supra/sub umbilical incision of 3 cm in order to find the caecum, which was to be mobilized. After that, the caecum was scratched using a sterile toothbrush on its front surfaces with an initial 2 cm x 2 cm lesion surface, as well as on a small section of the final ileum and on the corresponding mesentery. The abrasions continued to the point where small haemorrhagic elements appeared so as to induce the adhesions. The caecum was then placed in its anatomical area. The peritoneal cavity was

closed using continuous polyglycolic acid sutures 3/0 (Vicryl J and J Medical Limited, Ethicon Limited, UK). The animals were then released and left to recover.

During the insertion into the peritoneal cavity, special care was taken to avoid damage to the surrounding viscera as well as perforation of the intestinal wall itself. After 4 weeks, the animals underwent anaesthesia with ketamine and ether and, again, were subjected to laparotomy using the already existing incision. The peritoneal cavity and especially the periceacal area were evaluated macroscopically for the severity of adhesion development according to Nair classification, surface and tenacity of adhesions.

Resected caecal specimens were fixed in 10% formol solution. After histopathologic standard protocols, two slices of 3 μm in thickness were prepared by microtome from each specimen. Haematoxylin and eosin were used for assessing the severity of interstitial fibrosis, level of inflammation, tissue of necrosis, tissue oedema level of haemorrhagic lesion and neutrophils. The pathologist in the study group was blinded during the interpretation of the results.

Preparation of PRP Gel

Preparation of platelet-rich plasma gel was conducted by enriching whole blood platelet concentration using a two-step centrifugation procedure. A volume of 4.5 ml of blood was taken from each experimental animal mixed with 0.5 ml of sodium citrate as a precursor for the formation of PRP. The blood was centrifuged at 3000 rpm for 10 minutes at 20 degrees Celsius and then at 1500 rpm for 7 minutes (CL2 Biomet GPS). The PRP created was placed in the heating machine (Doctor Brown's 851) at 60 degrees for 5 minutes to convert the liquid into a gel which was then placed on the corresponding traumatic surface.

Macroscopic Assessment of Adhesions

In the second laparotomy, the type, extent, and tenacity of adhesions were assessed macroscopically, and the definitive adhesion score was determined by summing up three factors. The adhesions were reported to be in the abdominal, peri-caecal region.

Macroscopically, the type of adhesion was classified, according to Nair classification as follows: score 0= complete absence of attachment, score 1 = mild adhesion, one band /zone of adhesion between viscera or from a viscera to the abdominal wall, score 2 = moderate attachment, two zones either between the viscera or from the viscera to the abdominal wall, score 3 = severe adhesion, more than two zones between the viscera or between the viscera and the abdominal wall, score 4 or very serious adhesion with viscera directly attached to the abdominal wall.

The extent of adhesions was scored as follows: 0 = no adhesion, 1 = 1-25 % involvement, 2 = 26-50 %, 3 = 51-75 %, and 4 = 76-100 %. The tenacity of adhesions was evaluated as follows: 0 = no adhesion, 1 = separated from tissue with gentle handling, 2 = separated from tissue with moderate handling and traction, and 3 = requiring dissection with sharp instrument (*Figs. 1, 2, 3*).

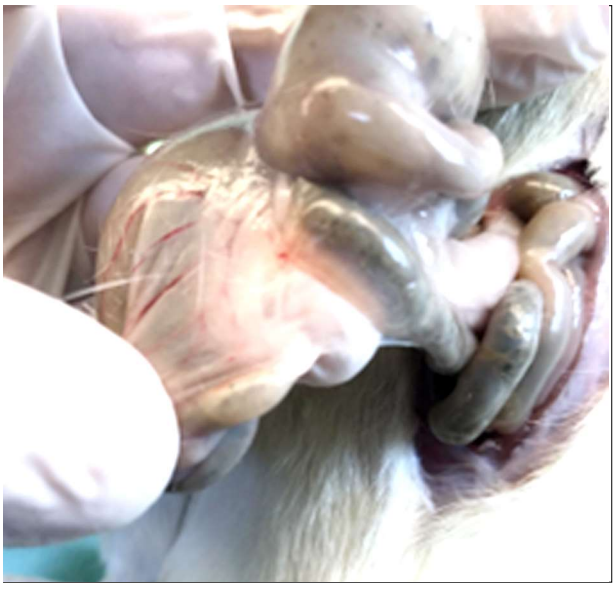


Figure 1. Post-operative results of Control Group (4 weeks after 1st surgery)



Figure 2. Post-operative results of Hyaluronic Acid Group (4 weeks after 1st surgery)



Figure 3. Post-operative results of PRP Group (4 weeks after 1st surgery)

Histopathological Evaluation

The histopathological examinations consisting of light microscopy analyses were carried out at the Pathology Department of the University of Athens. The samples obtained from the abraded caecal tissue and the adjacent peritoneal tissue were fixed in 10 % neutral buffered formalin solution for 2 days. Tissues were washed in running water and dehydrated with increasing concentrations of ethanol (50 %, 75 %, 96 % and 100 %). After dehydration, specimens were placed in xylene to obtain transparency and were embedded in paraffin. The embedded tissues were cut into 5 μm-thick sections and stained with haematoxylin, eosin and trichrome. Histopathological examinations were performed by a pathologist blinded to the study groups.

The severity of interstitial fibrosis was evaluated as follows: 0 = Absence, 1 = Mild, 2 = Intermediate, 3 = Severe. The level of inflammation was scored as follows: 0 = no inflammation, 1 = Mildly increased, 2 = Moderately increased. The degree of tissue necrosis, oedema and haemorrhagic lesions was graded as follows: 0 = absence, 1 = focal, 2 = diffuse. The neutrophils were evaluated as follows: 0 = within normal limits, 1 = mildly elevated 2 = moderately elevated.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics ver. 17 for Windows. The variables were described using frequencies and the corresponding percentages as well as frequency diagrams. In order to compare the variables of the three subgroups of the sample, the non-parametric Kruskal-Wallis test (for several independent samples) was used, accompanied by the non-parametric Mann-Whitney U test for two independent samples. The results were presented with their means ± standard deviation and represented with bar charts.

The non-parametric Spearman coefficient was used in order to detect linear correlations between the variables. The higher values of the coefficient the greater the correlation. In all cases, two-sided tests were used and there was a statistically significant difference or correlation when p-value was less than 0.05.

Results

Macroscopic

According to the analysis, the observed difference between the 3 groups, in terms of Nair classification, is statistically significant ($p < 0.001$).

Specifically, the group treated with hyaluronic acid shows significantly lower values than the control group ($p < 0.001$). Statistically significant difference also occurs between the group with the PRP treatment and the control group which has higher values ($p < 0.001$). On the contrary, hyaluronic acid and plasma (PRP) groups do not differ significantly. The extent and tenacity of adhesions differ significantly between the 3 groups ($p < 0.001$ in both cases).

In particular, PRP group shows a significantly smaller adhesion surface compared to control group ($p < 0.001$), as well as to the hyaluronic acid group ($p = 0.002$). The PRP group shows significantly lower adhesion tenacity, compared to the control group ($p < 0.001$) and the hyaluronic acid group ($p = 0.010$). Moreover, the group treated with hyaluronic acid shows less adhesion tenacity than the control group ($p <0.001$) (*Table 1*).

Microscopic

There is also a significant difference between the 3 groups, regarding the severity of the fibrosis and the level of the inflammation ($p = 0.007$ and 0.018 respectively).

Regarding the fibrosis, the difference is observed between the control group and the PRP group ($p = 0.015$). In the same way, for the level of the inflammation the difference is observed between the control group and the PRP group ($p = 0.021$). In both cases the values of the plasma treatment group are lower. There is also no significant difference between the control group and the hyaluronic acid group, neither between the two groups with the intervention.

The 3 groups have no significant difference, in terms of tissue necrosis, tissue edema, and the level of hemorrhagic lesions. Regarding the concentration of neutrophils, the 3 groups are significantly different ($p = 0.022$). The difference is observed between the control group and the PRP group ($p = 0.021$), with the latter showing lower values.

The differences between the control and the hyaluronic groups, as well as between hyaluronic and PRP groups are of no significance.

According to the study, the Nair scale is significantly correlated with surface area and tenacity of adhesions, with a strong positive correlation ($rho = 0.836$, $p < 0.001$ and $rho = 0.902$, $p < 0.001$ respectively). The association of the Nair scale with fibrosis severity, level of inflammation, and neutrophils is moderate ($rho = 0.634$, $p = 0.001$, $rho = 0.426$, $p = 0.038$ and $rho = 0.477$, $p = 0.018$ respectively). Namely, the higher the score of the Nair scale, the greater the surface area and the tenacity of the adhesions. Additionally, the higher the severity of the interstitial fibrosis, the level of inflammation and neutrophils, the higher the Nair score.

The area of the adhesions is significantly associated maintaining a strong positive linear correlation with the tenacity of the adhesions ($rho = 0.765$, $p < 0.001$). It is also associated with a positive correlation with fibrosis severity ($rho = 0.642$, $p = 0.001$), level of inflammation ($rho = 0.599$, $p = 0.002$), and neutrophil count ($rho = 0.534$, $p = 0.007$). These correlations are moderate in strength. In other words, the larger the surface of the

Table 1.

	Control Group	HA Group	PRP Group	P
Nair Classification	3.25 ± 0.707	1.38 ± 0.518	0.63 ± 0.744	<0.001
Adhesion Extension (%)	2.25 ± 0.463	1.75 ± 0.463	0.50 ± 0.535	<0.001
Tenacity of Adhesions	3.00	1.50 ± 0.535	0.50 ± 0.535	<0.001

adhesions, the higher the scores in the other parameters.

Adhesion tenacity is related to a moderate positive linear correlation with fibrosis severity (rho = 0.590, p = 0.002), level of inflammation (rho = 0.442, p = 0,030), and neutrophil count (rho = 0,586, p = 0,003). In this case, a higher adhesion tenacity corresponds to a higher severity of fibrosis and a higher level of inflammation and neutrophils.

The level of inflammation is also significantly related to a positive linear correlation of moderate strength, the degree of tissue necrosis and the level of neutrophils (rho = 0.449, p = 0.028 and rho = 0.563, p = 0.004).

We also observed a significant positive linear correlation between the levels of haemorrhagic lesions, the degree of tissue necrosis (rho = 0.426, p = 0.038) and the level of tissue oedema (rho = 0.408, p = 0.048). The strength of the relation is moderate (*Table 2*).

Discussion

Intra-abdominal formation of adhesions continues to be a burdening complication for patients who have had surgery. Visceral trauma, such as surgical invasion, initiates a cascade of sequential events, which are healing components, such as bleeding, inflammation, and tissue remodelling. This healing process necessitates the participation of growth factors and cytokines, which induce coagulation, cell proliferation, and angiogenesis to promote tissue regeneration. However, there is a delicate balance between the tissue injury and regeneration that controls the formation of adhesions.

During emergency as well as elective abdominal surgery, adhesion may occur and result in small-bowel obstruction, challenging revision operation, chronic abdominal and pelvic pain as well as female infertility. Additionally, adhesiolysis during re-operation increases operating time as well as recovery time subjecting the patient to significant risk of haemorrhage, visceral damage such as iatrogenic injury to the bladder, enterocutaneous fistulas, and potential resection of damaged bowel (15). Ellis H et al. with a retrospective cohort study with a follow-up period of 10 years proved that almost 6% of more than 20,000 cases reviewed were readmitted due to adhesion-related complications. Unfortunately, the rate exceeded 30% when "possibly adhesion related" complications were evaluated (16). Since this complication should not be underestimated, a number of preventive and therapeutic modalities has been described.

These range from surgical techniques to optimizing laparoscopy conditions, pharmacology interventions aimed at the inflammatory response and the use of agents that provide a physical barrier to adhesion formation. While these strategies have provided a satisfactory level of evidence, none have yet been proved totally successful in abolishing adhesions (17). In the present experimental study, we choose to administer PRP and Hyaluronic acid as a preventive treatment for rat abdominal adhesions.

Platelet concentrates are blood components separated from unusable elements (mostly the red blood cells, which are heavy and easily separated) through centrifugation. Hence,

Table 2.

	Control Group	HA Group	PRP Group	P
Severity of interstitial fibrosis	1.25 ± 0.463	0.88 ± 0.354	0.38 ± 0.518	0.007
Level of inflammation	1.63 ± 0.518	1.25 ± 0.463	0.88 ± 0.354	0.018
Tissue Necrosis	0.25 ± 0.463	-	-	N.S.
Tissue Edema	0.88 ± 0.354	0.75 ± 0.463	0.63 ± 0.518	N.S.
Level of hemorrhagic lesions	0.50 ± 0.535	0.25 ± 0.463	0.25 ± 0.463	N.S.
Neutrophils	1.50 ± 5.35	1.00 ± 0.535	0.50 ± 0.756	0.022

N.S.: Non Significant

elements such as fibrinogen/fibrin, platelets, growth factors, leukocytes may be quite useful in therapeutic applications. To be specific, all these extracts of the blood circulating tissue can induce proliferation of various growth factors, such as transforming growth factor b, insulin-like growth factor, and vascular endothelial growth factor, as well as migration and autocrine release of hepatocytic growth factors (18). Moreover, the formation of fibrin matrix also provides a suitable base for infiltrating cells that induce and accelerate fibroplasia and reducing the presence of free radicals. As indicated above, we focussed on the assumption that the topical use of PRP gel can reduce abdominal adhesion not by fibrin scaffold, but also by a variety of growth factors released from platelets. International studies have shown significant reduction in total adhesion score among rats with prophylactic PRP treatment, mainly in uterine horn models. In this study, authors found similar results as PRP gel reduces abdominal adhesions in rat Intestinal models.

On the other hand, hyaluronic acid, initially, isolated and purified by Meyer et al (19), from bovine vitreous in 1934, exhibits excellent physical and biological properties as an anti-adhesive agent. As an important component of extracellular matrix, hyaluronic acid influences migration, proliferation as well as differentiation of cells (20). This high-density polymer mucopolysaccharide improves tissue hydration by binding to water molecules, enhances cell resistance to mechanical injury while it reduces post-traumatic granulation tissue and fibrous formation (21). Moreover, hyaluronic acid is biocompatible, biodegradable (completely degrades within 5 days), and non-toxic, which enhances its popularity as a barrier agent (22,23). Adding to its physical properties, such as covering the wound surface, hyaluronic acid suppresses postoperative and inflammatory bleeding, reduces fibrin formation on the tissue contact surface and presents several anti-inflammatory effects (24).

Recent studies have examined the preventive effect of hyaluronic acid gel on intrauterine adhesion. In particular, Huberlant Stephanie H. et al. demonstrated that the use of hyaluronic acid gel in animal models reduced the incidence of intrauterine adhesion. In the same therapeutic approach, the application of hyaluronic acid gel after intrauterine adhesion separation has been found to significantly improve the pregnancy rate (25).

According to our results, PRP and hyaluronic acid present a beneficial role in reducing adhesion formation as both molecules turn out to be capable of reducing both macroscopic and microscopic parameters. Additionally, no statistical difference was detected between PRP and hyaluronic acid groups in many of the results. It is worth mentioning that the percentage of adhesion surface and adhesion tenacity is significantly reduced in the PRP versus the hyaluronic acid group.

Peritoneal adhesion carries a high burden of morbidity to the patients, as well as cost to the health service, therefore measures must be taken to help reduce its incidence. Prophylactic administration with PRP could represent a simple yet effective means of improving such an outcome, and this study provides a basis upon which future trials can assess the efficacy of prophylactic supplementation in practice.

Conclusion

In summary, when adhesion formation oxidative and inflammatory response is induced, PRP gel and Hyaluronic Acid protect against injury without having any detected adverse effects. Furthermore, even though both enzymes showed similar effects, only PRP was associated with reduced adhesion tenacity and surface. This may bring about future long term protective effects against intestinal adhesion. Nevertheless, further studies in intestinal adhesion are required for validation of a therapeutic scheme.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethical Statement

The protocol was approved by Veterinary Service of the Prefecture of Athens (ref. no. 5175 - June 07).

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