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Original Article

Possible Neoplastic or Proliferative Effects of Intra-Tympanic Platelet-Rich Plasma on the Middle Ear Mucosa: A Myth or a Fact to Consider?

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BACKGROUND: Platelet-rich plasma is a frequently used plasma-derived material; however, a possible neoplastic or proliferative effect is one of the limiting issues in its use. The aim of our experimental study was to investigate the long-term histological effects of platelet-rich plasma on the middle ear mucosa.

METHODS: The rats were divided into 2 groups randomly (groups 1 and 2). Group 1 represented the control group and 8 rats were included in this group. To the left ear, 0.3 mL of normal saline solution was administered intra-tympanically. No injections were done to the right ears. Group 2 represented the platelet-rich plasma group and 11 rats were included. To the left ears, 0.3 mL of platelet-rich plasma and to the right ears 0.3 mL of normal saline solution was administered intra-tympanically. The intra-tympanic platelet-rich plasma injections were done twice with an interval of 1 week. All animals were sacrificed in the third month. The degree of mucosal thickness, the presence of metaplasia, atypical cells, myofibroblastic infiltration, angiogenesis, and acute or chronic inflammation were evaluated histopathologically.

RESULTS: Histopathological findings in the right and left ears in each group were compared in itself. The degree of inflammation and mucosal thickness were significantly higher in the perforated and saline administered side, in group 1 ($P < .001$). In group 2, the degree of angiogenesis was significantly higher in the platelet-rich plasma administered side ($P < .001$). The degree of mucosal thickness was significantly higher in the saline administered side ($P < .001$).

CONCLUSION: Considering the anti-inflammatory and regenerative features and its safety, intra-tympanic-PRP may, in the future, be an alternative to current intra-tympanic treatment modalities.

KEYWORDS: Platelet rich plasma, middle ear mucosa, otology, injection, intra-tympanic

INTRODUCTION

Platelet-rich plasma (PRP) is a plasma component that contains a higher platelet concentration than the whole blood and it is derived by centrifuging the whole blood. Platelets are responsible for hemostasis, construction of new connective tissue, and revascularization. In order to fulfill its tasks in these pathways; platelets synthase and secrete many different peptides and growth factors.[1]

Based on the self-healing potential of the human body, high concentrations of platelets and the linked growth factors have been used in many different areas of medicine since 1970s.[2] The clinical use of PRP started with an open-heart surgery and yet it is still being used in orthopedic surgery, neurosurgery, plastic surgery, dermatology, and otolaryngology as well.[3]

The increasing utility of PRP in medicine has brought along safety concerns at the same time. Compared to its positive effects on regenerative medicine, the possible oncogenic potential of PRP is a less studied concept. There is a conflict in the literature in terms

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of the possible oncogenic potential of PRP. Some authors disagree with the oncogenic potential because of the fact that all growth factors act on cell membrane, not the nucleus. Therefore, they promote normal gene expression.[4] Since cancer and wound healing have several similarities in terms of cellular and molecular mechanisms, some authors, on the other hand doubt that PRP is totally safe.[5]

Unlike other surgical fields, otolaryngology is an area where PRP use is limited. Knowledge about the proliferative or neoplastic effects of PRP on the external ear and the middle ear mucosa is not much in the literature.[3] The aim of our experimental study was to investigate the long-term histological effects of intra-tympanic (IT)-PRP on the middle ear mucosa in an animal model.

MATERIALS AND METHODS

The experimental study was done in line with the experimental ethical guideline and animal conservation laws and national regulations in our country. All experimental protocols were confirmed by Health Sciences University of Turkey, Ankara Training and Research Hospital Local Animal Experiment Ethics Committee, Turkey (prot. number: March 14, 2019/0052-574). All procedures were performed humanely below with the principle for an animal experiment at the Department of Laboratory Animal Science of Medical School. The animals were kept in polypropylene cages with free reach to ordinary pellet diet and water. They were kept in a temperature-controlled (20°C ± 2°C) and humidity-controlled (60% ± 5%) room with 12 hours light/dark cycle. The animals were isolated and acclimated in the laboratory room for a week.

Surgical Procedure

In this experimental study; 21 male Wistar albino rats weighing 250-300 g, aged 10-11 weeks were used. They were anesthetized with ketamine hydrochloride (100 mg/kg, Ketalar, Parke-Davis, Turkey) by intramuscular injections.

Initially, 2 rats were sacrificed in order to collect intracardiac blood. The blood was collected in tubes with ethylene diamine triacetic acid. Liquid PRP was prepared with the double centrifuge method previously defined in our hospital by Duymus et al.[6] The ideal working definition of PRP which has been previously defined in various studies as approximately 2.5- to 5-fold of normal blood platelet count,[6,7] was obtained in our liquid PRP preparation.

Both tympanic membranes of the rats were evaluated under an oto-microscope (Opmi 1, Zeiss, Germany) following anesthesia and rats with normal tympanic membranes were included in this study. The rats were divided into 2 groups randomly (groups 1 and 2). Group 1 was designed in order to assess the possible effect of paracenteses on the middle ear mucosa and 8 rats were included in this group. To the left ear, 0.3 mL of normal saline solution was administered IT under an oto-microscope with a 22-gauge needle. No injections were done to the right ears.

Group 2 was designed to assess the possible effects of PRP on the middle ear mucosa and 11 rats were included. To the left ears, 0.3 mL of PRP and to the right ears 0.3 mL of normal saline solution was administered by IT injections under an oto-microscope.

The IT-PRP injections were performed twice with an interval of 1 week.

Oto-microscopic and Histopathological Examination

All animals were sacrificed without pain by high dose pentobarbital (80 mg/kg, intraperitoneal injection) in the third month. The temporal bulla of both sides was taken out from all the sacrificed animals. The histopathological evaluations were done by 1 pathologist with a light microscope, blindly. The specimens were fixed with 10% buffered neutral formalin and later on decalcified with 10% ethylene diamine tetra acetic acid. After embedded in paraffin, sections of a thickness of 5 μm were prepared and stained with hematoxylin–eosin. A high-resolution light microscope (Olympus DP-73 camera, Olympus BX53-DIC microscope; Tokyo, Japan) was used to evaluate the specimens. The evaluation was done by 40×- to 100×-fold magnification.

The degree of mucosal thickness, the presence of metaplasia, atypical cells, angiogenesis, and acute or chronic inflammation were evaluated histopathologically.

The measurement of the mucosal thickness was carried out with the computerized microscopic images with a camera (Olympus BX50, Olympus Optical Co., Tokyo, Japan). The measurement of mucosal thicknesses was done by micrometers. Measurements were done in 10 different areas and the mean value was accepted as the mucosal thickness. The mucosal thickness was graded as (+) when it had increased less than 10%; (++), when more than 10% but less than 25%; (+++),when it had increased by 25% or greater.

Epithelial metaplastic changes were accepted as the transformation of the normal epithelium to a respiratory or stratified squamous epithelium. The mentioned changes were graded as (+) if this metaplastic epithelium accounted for more than 50% of the epithelium observed.

Specimens in which pleomorphism, indistinct boundaries, hyperchromatism and mitosis were present, were accepted as atypical cells. The specimens were scored subjectively as (+) for presence of an atypical cell and (–) for the absence of an atypical cell. A single atypical cell represented a (+) specimen.

Angiogenesis was scored by the number of vascular lumens seen in each field. It was graded as (+) when the vascular lumen number increased less than 10%, (++) when greater than 10% yet less than 25% and (+++) when greater than 25%.

Acute or chronic inflammation, myo-fibroblastic infiltration, and collagen deposition were graded subjectively as (+) or (–).

Statistical Analysis

The statistical analyses were done by using Statistical Package for the Social Sciences (SPSS) version 15.0 software program (SPSS Inc.; Chicago, IL, USA) and a value of $P < .05$ was accepted as significant.

Eight rats in group 1 (16 ears) and 11 rats in group 2 (22 ears) were in included in the analysis. Pearson chi-square test and Fisher's exact test were, where appropriate, used to investigate the association between categorical variables of the degree of mucosal thickness, the presence of angiogenesis, and acute or chronic inflammation in each group.

Table 1. The Comparative Table of Histological Parameters in Groups 1 and 2

Group	Number	Ear	Mucosal thickness			Angiogenesis			İnflammatory cells		Myofibroblastic infiltration		Epithelial metaplasia		Atypia	
			+	++	+++	+	++	+++	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)
Group 1	8	Right	0	0	0	0	0	0	8	0	8	0	8	0	8	
	8	Left	3	0	0	0	0	0	5	3	8	0	8	0	8	
Group 2	11	Right	3	0	0	0	0	0	9	2	11	0	11	0	11	
	11	Left	0	0	0	4	2	0	10	1	11	0	11	0	11	

Statistically significant histopathologic changes, $P < .05$.
Group 1: Right, no injections; Left, saline injected group.
Group 2: Right, saline injected group; Left, PRP injected group.
PRP, platelet-rich plasma.

RESULTS

The histopathological findings in the right and left ears in each group was compared in itself. Table 1 summarizes the results of histopathologic examination in both groups.

In group 1, no mitotic cells, metaplasia, or myofibroblast and collagen formation were detected in either side of ears (Figure 1). The degree of inflammation (Figure 2) and mucosal thickness were significantly higher in the left perforated side where saline solution was administered ($P < .001$).

In group 2, similar with group 1, no mitotic cells, metaplasia, or myofibroblast and collagen formation were detected in either side of ears. Angiogenesis was determined as, in 4 ears less than 10% and in 2 ears greater than 10% yet less than 25%. The degree of angiogenesis was significantly higher in the left side where PRP was administered ($P < .001$) (Figure 3). The degree of mucosal thickness was significantly higher in the right side where saline infusion was administered ($P < .001$). Inflammatory response of the middle ear mucosa was seen more in the right side but there was no statistically significant difference in terms of inflammation between the left and right ears ($P = .621$)

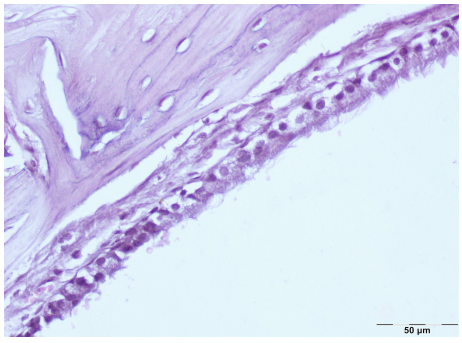

Figure 1. Normal middle ear mucosa, a section from the right side in group 1.

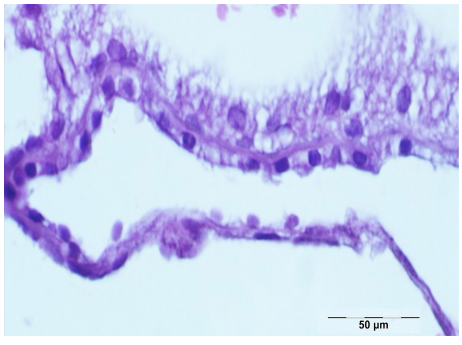

Figure 2. Inflamed middle ear mucosa, a section from the left side in group 1.

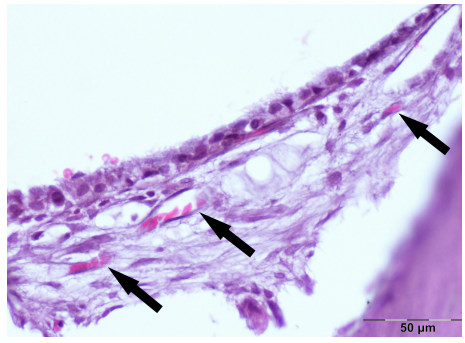

Figure 3. Multiple angiogenetic focuses (black arrows) detected on the left side where PRP was administered in group 2. PRP, platelet-rich plasma.

DISCUSSION

Platelet-rich plasma is basically a plasma volume of intense platelet count. Although different concentrations may be obtained, an efficient PRP solution should contain 2.5- to 5-fold of normal blood platelet count.[6,7] Platelets are one of the cellular components of the circulating blood. Apart from its crucial role in hemostasis, platelets also release special peptides, growth factors, immune system messengers, enzyme inhibitors, and other bioactive compounds which later on induce tissue repair, angiogenesis and regulate inflammation.[8]

As being the first cell group to respond acute injury, platelets have a key-role in regulating the inflammatory process.[9] Many growth factors are released from platelets that affect the inflammatory process and promote tissue regeneration or healing. Platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and hepatocyte growth factor are the growth factors that are secreted from platelets.[10]

Platelet-derived growth factor-ab and PDGF-bb, 2 elements of PDGF family, have strong mitogenic effects on stem cells and osteoblast and they enhance tissue repair by promoting angiogenesis and collagen synthesis.[10] Similarly, EGF has also a mitogenic effect on especially epithelial cells. Vascular endothelial growth factor is another secreted element of PRP that enhances tissue repair by causing endothelial differentiation which results in angiogenesis. Transforming

growth factor, perhaps one of the most important elements in tissue regeneration, controls the production of the extracellular matrix. In addition, Lynch et al[11] demonstrated that increased production of collagen and fibronectin were a result of local administration of TGF.

Since its first clinical use in 1970s, PRP has gained popularity up to date. As in many different aspects in medicine, studies involving the effects of PRP on otologic surgery have started to emerge.[3] Erkilet et al[12] conducted a study in which PRP administration on tympanic membrane perforations led to an improved healing time.[12] Özgürsoy et al. [13] in another study, concluded that PRP was an effective autologous material for the healing process of acute tympanic membrane perforations in a rabbit model. Positive effects of using PRP was also demonstrated on fat grafts used for fat myringoplasty.[14] An improved healing rate and time in myringoplasty were recorded in several recent studies.[12,15]

Recently, several studies have been published in the literature that showed promising effects of PRP in neural healing also. Li. et al[16] conducted a study in which PRP had positive effects on facial nerve trauma by improving Schwann cell and axon recovery.[16] In another recent study of Stolle et al.[17] PRP was stated to promote neuroprotective and regenerative effects on spiral ganglia neurons when administered in adequate concentrations. Insulin-like growth factor-1, which is one of the active substances of PRP content, has also been studied lately for its proliferative and protective effects on spontaneous sensorineural hearing loss and ototoxicity. In the study, it was concluded that the IT injections of IGF-1 had an effect of controlling and reversing sensorineural hearing loss.[18]

The utilization of IGF and autogenic PRP, containing various growth factors, are gaining popularity in the field of otology. Instead of using a single growth factor, PRP, which is an inexpensive and native bio-active material containing multiple growth factors may also be used.[4] The curative effects of both PRP and the growth factors that it contains have been investigated on local applications on the Tympanic Membrane (TM), middle ear, and inner ear. However, the possible neoplastic effect is an issue that is not revealed yet.[3,17,18]

The intense use of PRP in contemporary medicine has brought along safety concerns as well. As being an autologous product there is no risk of infection. Adverse reactions due to PRP are extremely rare. In the literature, there is a single novel case report of serum sickness disease which later on led to Meniere's disease.[19]

In our experimental animal study; we aimed to investigate the effects of intratympanic PRP use on the non-traumatic healthy middle ear mucosa as there is no similar study in the literature as far as we are concerned. In group 1, in order to assess the possible effects of paracentesis which was done twice, on the middle ear mucosa in a period of 3 months, while preserving the right ear, we administered saline solution to the left ear. At the end of 3 months, there were no histopathological changes in the preserved side however on the left side where perforation was done and saline solution was administered, an increase in mucosal thickness and inflammation were observed and these were found statistically significant ($P < .001$). This result indicated us that perforation of TM may cause inflammatory reaction. The TM perforation alone may be the triggering factor of inflammation.[20]

In group 2, PRP administration, in long term, did not cause an increase in mucosal thickness in the middle ear mucosa. The degree of mucosal thickness was significantly higher in the saline administered right side. Metaplastic or mitotic cells and significant inflammatory response were not observed on the PRP administered left side. Angiogenesis was observed only in the left side in which PRP was administered and the difference was found statistically significant ($P < .001$). We did not observe any adverse effect due to PRP use. The angiogenesis observed in the PRP group was in accordance with the current literature. In this group, more inflammation was present in the saline administered side though it was not statistically significant. The relatively restricted number of the animals used in this study may have contributed to this result. Future studies designed with larger numbers of animals may demonstrate a statistically significant difference in this aspect. It is a well-known fact that PRP, with its content of various growth factors may regulate the inflammatory response.[10]

As it is known, PRP induces endothelial cell proliferation and angiogenesis that are crucial steps in normal development; wound healing, recovery from ischemic disease, and organ regeneration.[21] Mamaoto et al have demonstrated that, with its content of angiotensin-1 and other angiogenic factors, mouse PRP extract, stimulates endothelial cell growth, migration, and differentiation in cultures of human dermal microvascular endothelial cells.[22] In our study, the increased vascularization in the mucosa observed after the administration of IT-PRP supports this idea.

A possible oncogenic effect of PRP has been a subject to debate in the literature. Marx argues that no growth factor can provoke cancer. As growth factors act not on the nucleus but on the cell membrane, they only promote normal gene expression.[4] Omar et al[5] concluded an experimental animal study in dorsal muscle injury with prolonged use of PRP and stated that according to their data, long term PRP use did not cause any special considerations regarding tumor growth.

On the other hand, it is a well-known fact that growth factors play an essential role in tumor angiogenesis which than result in tumor progression and metastasis. There is no evidence regarding the use of PRP in cases with dysplastic and tumoral tissues.[23,24] Menter et al. stated that platelets and their interaction with cancer cells is actually how the metastatic process initiates. They also concluded that platelets and their interactions may lead to a progression of pre-malign lesions.[25] It must be kept in mind that none of the mentioned studies above involve the field of otology.

In respect to other studies in this field, as Marx et al., we share the similar opinion that IT-PRP does not provoke cancer and especially when used in the middle ear. According to our findings IT-PRP has no neoplastic or proliferative effects though further experimental and clinical studies are needed in order to make a precise judgement.

Apart their regenerative effects on various tissues, knowledge about the effects of PRP and related growth factors on the middle ear mucosa is limited. In our study we have observed that IT-PRP, which contains various GFs and bioactive proteins, stimulated angionesis and showed anti-inflammatory effects as limiting the mucosal thickness on the middle ear mucosa though no neoplastic or proliferative effects were observed.

CONCLUSION

Platelet-rich plasma is practical and in many conditions a useful autogenic material. According to our findings, its prolonged use in the middle ear is safe for the middle ear mucosa, though more studies are needed in this area. When considering the anti-inflammatory and regenerative features and its safety, local administration of PRP may, in the future, be an alternative or at least a subsidiary treatment in otology practice.

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