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EFFECTS OF THE PLATELET RICH PLASMA ON APEXOGENESIS IN YOUNG MONKEYS: RADIOLOGICAL AND HYSTOLOGYCAL EVALUATION

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Platelet-reach plasma (PRP) is an attractive tool in regenerative medicine due to its ability to stimulate proliferation and differentiation of stem cells. Since dental pulp derived stem cells are recognized as central in apexogenesis, the aim of the study was to evaluate radiologically and histologically effects of PRP on apexogenesis in teeth with immature roots. The study included eight monkeys (Cercopithecus Aethiops) divided in two equal groups for evaluation 3 and 12 months after treatment. All participants obtained the same treatment including pulpotomy and after-treatment with: hydroxiapatite (HA)-incisor and HA+canine PRP. Radiological evaluation was performed using the long cone paralleling technique for recording of defined parameters and histological evaluation was performed using tissue removed en block for the observation of parameters related to apexogenesis. The results obtained radiologically and histologically have shown increase in bridge formation in HA+PRP (75%) group after 3 months comparing to HA group (50%). Contrary to that, after 12 months there were no significant differences between groups. The root delay was not registered in the HA+PRP group contrary to HA group where it was registered in 25% after 12 months. Results of the study suggest that PRP is a powerful tool for intensive and rapid apexogenesis since it offers clear and comprehensive results (mostly in the first three months) which are early radiologically visible without any failure in the proposed requests.

Key words: apexogenesis, growth factors, hydroxyapatite, platelet rich plasma, PRP, regeneration

INTRODUCTION

Apexogenesis represents the process of development and formation of the root apex under physiological conditions and under regenerative therapy procedures, as well. This process is crucial in the determination of further destiny of teeth with injured pulp. The main tendencies of regenerative apexogenesis is a preservation of the pulp vitality since it is reported that only dentin pulp might be

used as a source of progenitor cells with potential for the regeneration of the dentin-pulp complex (Tziafas and Kodonas, 2010). Formation of the dentin bridge is also an important part since it confirms vitality of the pulp together with the maintenance of Hertwig's epithelial root sheath that enables longitudinal growth of the tooth. Accordingly to recent science, post-neonatal stem cells have the ability of self-renewal and proliferation with multidifferentiation potential to give multiple specialized cell lineages such as components of pulp-dentin and cementum-periodontal ligament complexes together with growth factors as their major regulators are found to be the targets in regenerative medicine of apexification and apexogenesis (Friedlander *et al*., 2009; Huang *et al*., 2009). These stem cells were isolated from dental pulp, apical papilla and periodontal ligament, and stem cells originated from the dental pulp have shown the highest potential in regeneration of the pulp-dentine complex.

Platelet rich plasma (PRP) represents the attractive tool in current regenerative medicine, obtained by sequestering and concentrating platelets by gradient density concentration (Lekovic *et al*., 2003). This tool is in accordance with the contemporary concept of molecularly oriented biomedicine since it is based on extremely augmented concentrations of growth factors that affect stem cells and all other tissue components responsible for tissue regeneration. PRP gel originates from autologous plasma and represents modifications of fibrin glue obtained by mixing platelets and fibrinogen centrifuged from whole blood with thrombin and calcium chloride, containing an over threefold increased concentration of platelets than untreated blood (Marx *et al.*, 1998). Growth factors are biologic polypeptides that regulate cell multiplication, migration, and differentiation (Camargo *et al*., 2009) as the central process of tissue regeneration. The main growth factors contained in PRP are: PDGF, TGFβ, PDEGF, PDAF, IGF-1 and PF-4 and they are contained in the platelets' alpha granules (Camargo *et al*., 2002). By taking into consideration the importance of local stem cells stimulation by growth factors and the previously reported impact of PRP on hard and soft tissue healing, application of high concentrations of growth factors contained in PRP could be beneficial in apexogenesis (Arora *et al*., 2009).

During investigations of regenerative agents for apexogenesis, the choice of appropriate intra-canal medicaments as the medium represents an important part. Application of calcium hydroxide and related medicaments is contraindicated as they inhibit further root growth, contrary to hydroxyapatite (HA) that is reported to be successful in apexogenesis. HA renders direct adaptation of new calcificated tissue to the material without necrotic zone characteristic to materials based on Ca(OH)2 (Alliot-Licht *et al*., 1994; Tjäderhane *et al*., 2002) and it stimulates the formation of dentine bridge.

The aim of the study was to evaluate the effect of platelet rich plasma on apexogenesis in young monkeys by using histological and radiological analyzes.

MATERIALS AND METHODS

Experimental animals

The study included 8 young monkeys (*Cercopithecus Aethiops)*, with body weight of at least 1.5 kg; on average 3 years old and with incomplete root formation of permanent dentition. The study was approved by Animal Ethical Screening Comitee and the Ethical Commite of the Dentistry School of Belgrade University. The experiment was carried out in complete accordance with the European Communities Directive (86/609/EEC).

Material used in the study

The following preparations were used:

– Apatec®, Stomygen (commercial hydroxylapatite),

– PRP (prepared at the Torlak Institute).

Study design

All animals were pre-medicated with atropine sulphate (0,5 mg/kg body weight) and anesthetized with an intramuscular injection of Conbern® (0.005 mg/kg) Bayne, Germany and intravenous injection of Nembutal, Abbott Labs, Chicago USA (25 mg/kg) before procedures.

Canine tooth was chosen as experimental tooth for application of HA with PRP (HA+PRP), and one incisor tooth of the same animal was used as the control for application of HA alone. All treated teeth were exposed to the same procedure including isolation with cofferdam and washing with 0.5 % chlohexidine. After tooth prepairation, the cavity was made with air turbine and the pulp was removed using a sterile carbide round bur at the cement-enamel junction (pulpotomy). After that the pulp wound was recovered with appropriate material depending on the group affiliation, and the cavity was closed with glassionomer cement and amalgam. The radiographs and histological specimens were obtained from half animals chosen by randomization after 3 months and from the remaining animals after 12 months. The animals were sacrificed after sampling by using an overdose of Nembutal®.

PRP preparation

PRP was prepared using the method described by Weibrich *et al*. (2002). Whole blood 360 mL volume was centrifuged in the standard laboratory centrifuge (MSE, England) for 20 min at 1200 r.p.m. with Na-citrate. Platelets extracted from the red fraction were resuspended and concentrated by further centrifugation (2000 r.p.m. for 15 min). After serum removal, concentrated platelets were ready for application.

Radiological analyses

Radiographs were obtained using long cone paralleling technique. Recording conditions were as follows: 35KV, 8mA with exposition time 0.02 sec.

The following parameters were recorded:

– Presence of dentine bridge,

– Delay of root development,
– Presence on intra-canal pathological formations (denticles and canal obliteration),
– Presence of peri-apical reaction,
– Root growth using Demirjian's system (Figure 1) (Demirjian *et al*., 1973).

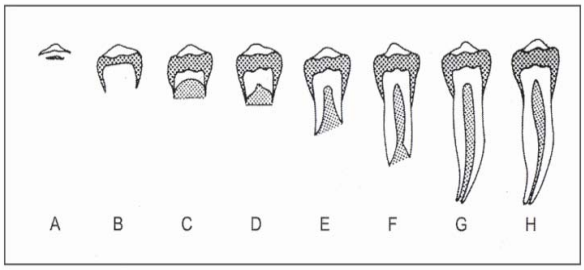

Figure 1. Demjrian's scale for root growth and tooth maturation

Histological analyzes

Histological specimens were taken in block including experimental teeth with surrounding bone following ISO usage guidelines (Technical Report 7405). Samples were fixed in 10% buffered formalin (pH=2), demineralized for 40-50 days in 5% trichloracetic acid and embedded in paraffin. Sections of 6 μm thickness were cut in the mesio/distal direction and mounted on glass slides. They were stained with haematoxylin and eosin, as well as with Gram for identification of bacteria, and analyzed microscopically (Carl Zeiss Inc., Oberkochen, Germany).

The following parameters were recorded:

– Presence and quality of dentine bridges i.e. the formation of tertiary dentine by newly differentiated odontoblast-like cells, at the site of pulp exposure (Murray *et al*., 2003). Differentiation between reactionary and reparative dentine was made during the examination of the sections: 1-new tissue barrier behind the applied material; 2-new tissue barrier distant from the applied material; 3-absence of tissue barrier.

– Pulp response on therapy: 1-normal tissue morphology in the region of exposed pulp tissue; 2-exposed pulp tissue is altered, but tissue under the exposed zone is normal; 3-loss of pulp morphology and altered tissue under the exposed zone ; 4-necrosis of at least one third of pulp.

– Inflammatory reaction: 1-without inflammatory cells or with a few inflammatory cells under the exposed zone; 2-polimorphonuclears (PMNs) or mononuclears (MNs) in the inflammatory zone; 3-enhanced inflammatory lesion overtaking third or more of pulp; 4-completely necrotic pulp.

Statistical analysis

Statistical analysis was performed using commercial statistical program SPSS (version 17.0). The data was tested for normality using Shapiro-Wilk and

Kolmogorov-Smirnov tests. In the analysis of histological data Wilcoxon test has been performed to assess the differences in mean for each parameter within groups. The Fisher test has been performed for the analysis of histological and radiological data.

RESULTS

Results of radiological evaluation of apexogenesis between groups in two temporal points are listed in Table 1. Formation of dentin bridges after 3 months was observed in 2 teeth (50 %) treated with HA and in 3 teeth (75%) treated with HA + PRP (Figure 2). Delay of root development was present in 2 teeth (50%) tested with HA and in 1 tooth (25%) treated with HA + PRP. Obliteration of the root canal or presence of denticles was not detected in the samples, and no periapical reaction was found. After 12 months formation of dentin bridges was found in 3 teeth (75%) treated with HA and in the same unchanged percentage in the HA + PRP group (75%). Delay of root development was present in 1 tooth (25%) treated with HA and completely absent in the HA + PRP group. Obliteration of the root canal or presence of denticles were not detected in the samples and no periapical reaction was found as well. Statistical analysis of obtained radiological parameters did not show any significant differences between groups (Table 2).

Histological evaluation of apexogenesis between groups in two temporal points is listed in Table 3. The presence of dentine bridges was evidenced in 75% of samples treated with HA + PRP after 3 months and after 12 months in the same percentage, also (Table 4). In HA samples dental bridges were present in 50% after 3 months, and in 75% after 12 months same as in the HA + PRP group (Table 4). Newly formed dentine bridges completely closed the dental pulp and achieved intimate contact with surrounding dentin (Figure 3). In the HA+PRP group after 3

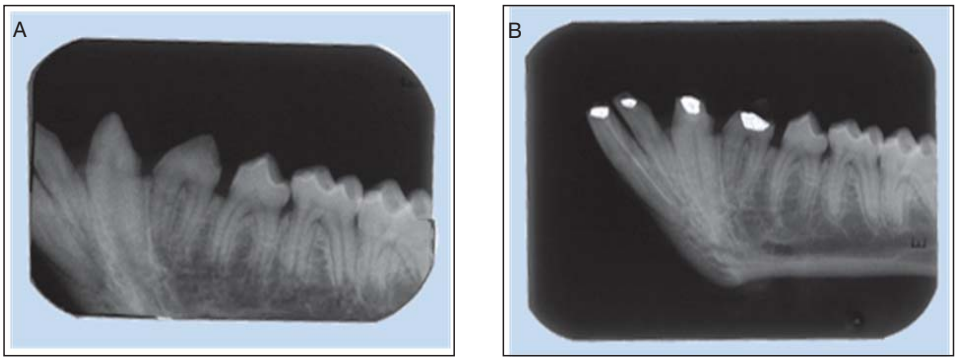

Figure 2. A - Mandibular right lateral incisor and canine before treatment B - Mandibular right lateral incisor and canine 3 months after treatment
A - Mandibular right lateral incisor and canine in stage F of root development
B - Mandibular right lateral incisor in stage G of root development 3 months after treatment with HA and mandibular right canine in stage H of root development 3 months after treatment with HA+ PRP treatment

Table 1. Radiological evaluation of apexogenesis between groups in two temporal points

Clinical parameters	Stage of development before the treatment	Observed parameters at 3 months control				Stage of development at 3 months control	Stage of development before the treatment	Observed parameters at 12 months control				Stage of development at 12 months control
		a	b	c	d			a	b	c	d	
HA+PRP	G	+	+	-	-	G	G	+	-	-	-	*H*
	F	-	-	-	-	G	F	-	-	-	-	H
	F	+	-	-	-	G	F	+	-	-	-	H
	F	+	-	-	-	H	F	+	-	-	-	H
HA	G	+	-	-	-	H	G	-	-	-	-	H
	F	-	+	-	-	G	F	+	+	-	-	G
	F	-	-	-	-	G	F	+	-	-	-	H
	F	+	+	-	-	G	F	+	-	-	-	H

a – presence of dentine bridge; b – retardation of root growth; c – obliteration of root canal and presence of denticles; d – presence of deformities in periapical region; + yes; – no

Table 2. Statistical analysis of radiological parameters

Observed parameters N (%)		Observed period			
		3 months		12 months	
		yes	no	yes	no
Presence of dentine bridge	HA	2 (50%)	2(50%)	3 (75%)	1 (25%)
	HA+PRP	3 (75%)	1 (25%)	3 (75%)	1 (25%)
Fishers test, significance		p=0.989		p=0.999	
Retardation of root growth	HA	2 (50%)	2(50%)	1 (25%)	3 (75%)
	HA+PRP	1 (25%)	3 (75%)	0 (0%)	4 (100%)
Fishers test, significance		p=0.608		p=0.989	
Obliteration of root canal and presence of denticles	HA	0 (0%)	4 (100%)	0 (0%)	4 (100%)
	HA+PRP	0 (0%)	4 (100%)	0 (0%)	4 (100%)
Fishers test		/		/	
Presence of periapical reactions	HA	0 (0%)	4 (100%)	0 (0%)	4 (100%)
	HA+PRP	0 (0%)	4 (100%)	0 (0%)	4 (100%)
Fishers test		/		/	

Table 3. Histological evaluation of apexogenesis between groups in two temporal points

Observed parameters N (%)		Observed period			
		3 months		12 months	
		HA	HA+PRP	HA	HA+PRP
Inflamatory reaction	1	1 (25%)	2 (50%)	3 (75%)	3 (75%)
	2	3 (75%)	2 (50%)	1 (25%)	1 (25%)
	3	/	/	/	/
	4	/	/	/	/
Fisher's test; significance		p=0.608		p=0.989	
Pulp response on applied therapy	1	/	/	/	1 (25%)
	2	3 (75%)	4 (100%)	3 (75%)	3 (75%)
	3	1 (25%)	0 (0%)	1 (25%)	/
	4	/	/		
Fisher's test; $\chi 2$; significance		p=0.467		p=0.215	
Presence and quality of dentine bridge	1	2 (50%)	3 (75%)	3 (75%)	3 (75%)
	2	/	/	/	/
	3	2 (50%)	1 (25%)	1 (25%)	1 (25%)
Fisher's test; significance		p=0.608		p=0.989	

Table 4. Statistical analysis of histological data within the same group in two temporal points

Observed parameters N (%)		Used matherials			
		HA		HA+PRP	
		3 months	12 months	3 months	12 months
Inflamatory reaction	1	1 (25%)	3 (75%)	2 (50%)	3 (75%)
	2	3 (75%)	1 (25%)	2 (50%)	1 (25%)
Wilcoxon's test, significance		p=0.025		p=0.083	
Pulp response on applied therapy	1	/	/	0 (0%)	1 (25%)
	2	3 (75%)	3 (75%)	4 (100%)	3 (75%)
	3	1 (25%)	1 (25%)	/	/
Wilcoxon's test, significance		p=0.317		p=0.157	
Presence and quality of dentine bridge	1	2 (50%)	3 (75%)	3 (75%)	3 (75%)
	3	2 (50%)	1 (25%)	1 (25%)	1 (25%)
Wilcoxon's test, significance		p=0.083		p=0.317	

months increased density of osteoblasts-like cells and greater thickness of dentin bridges were recorded. In the samples treated with HA+PRP a higher density of odontoblast like cells compared to samples treated with HA was observed (Figure 4). In all analyzed specimens after 3 months odontoblasts were found with some kind of structural changes in the form of elongated, cylindrical cells. They were noticed at the site where the pulp was exposed while other tissue structures were preserved. Morphological changes of the tissue were less pronounced in the HP+PRP group. Data analysis did not show any significant differences between groups ($p>0.05$) (Table 4) and the only significant difference was found in the decrease of inflammatory reaction in the HA group between the third and 12th month ($p=0.025$). The inflammatory infiltrate was predominantly composed of

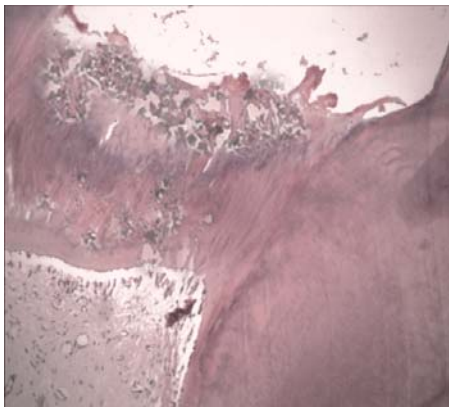

Figure 3. Compact formation of dentine bridge in HA+PRP specimen, that completely close dentine pulp and achieve contact with surrounding dentin (Hemacolor staining, magnification 100x)

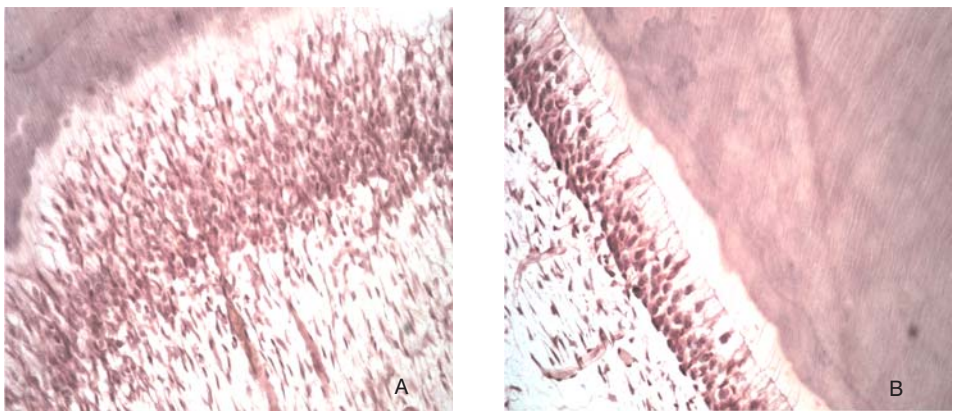

Figure 4. Higher density of odontoblasts in HA+PRP specimenn (A) in comparison to HA specimen (B) (Hemacolor staining, magnification 100x)

lymphocytes, plasma cells and macrophages. Severe chronic inflammation, massive infiltration of neutrophils with abscess formation was not identified in any sample. In both groups after 12 months completion of root and periodontium formation was observed. Presence of Gram-bacteria was observed by gram staining only in dentin. Bacteria were not present in the pulp of any sample.

Presence of dentine bridges was the parameter that we analyzed in both investigations, and formed dental bridges were observed in the same percent (75%) in radiological and histological procedures. In higher percent, dentine bridge was formed earlier in group where HA + PRP was applied than in group HA (75% and 50%, respectively).

DISCUSSION

Apexogenesis represents the real clinical challenge in current dentistry since it is of essential significance for complex dental prognosis. Recent investigations are oriented to regenerative methods since the treatment with previous medicaments did not lead to stimulation of pulp tissue regeneration as a source of target stem cells responsible for the process of apexogenesis. The principle of regenerative medicine is to mimic physiological events of development, so we treated the injured pulp directly with an increased concentration of growth factors with the aim to preserve pulp vitality by self-regeneration and by self-protection indirectly by stimulating odontoblasts to produce a reparative barrier, thereby to stimulate apexogenesis. One of the main beneficial characteristics of PRP is their autologous origin with complete biocompatibility which excludes additional inflammatory reactions to exogenous material that could potentially move the regeneration into an excessive direction.

By considering our findings we can conclude that PRP strongly stimulates pulp activity since the specimens from HA+PRP group were characterized by increased odontoblast density with consequentially more compact reparatory bridges (they were thicker and more regular morphologically) and the newly created dentin was more regular with a decrease of fibrous cell inclusions. Additionally, reparatory bridges were found in greater percentage after three months in PRP treated teeth (75%) than in the HA group (50%). Thereby, the pulp was preserved successfully which was additionally confirmed by complete absence of bacteria in the pulp tissue, contrary to their presence in the dentine of the same tooth which is important in avoiding infection that could result in arrested root development (Kvinnsland *et al*., 2010). Formation of dentine bridges is found to act as a deposit of growth factors so its role is not only as a barrier, but as a stimulator of regenerative processes, as well (Tziafas *et al*., 2000). These findings suggests that PRP derived growth factors were stimulated differentiation of pulp stem cells into odontoblasts and that is in correspondence with findings of Friedlander *et al*. (2009). The fibrin component of the PRP may contribute in stabilization of the blood clot which is additional source of growth factors (Wikesjo *et al*., 1992).

The early evidenced radiological signs (not only histological) of dentine bridge formations (after 3 months) in HA+PRP group suggests the powerful

potential of PRP. In addition, the smaller percentage of root delay found in this group supports this assumption and these facts are in correspondence with findings of Lee *et al*. (2011) who have shown that PRP treatment enhanced proliferation and mineralization of dental stem cells. In general, radiological parameters between HA+PRP and HA group became equal in the 12th month contrary to the third month when apexogenesis was more expressed in the PRP group which indicates that PRP derived growth factors accelerate and intensify the process of apexogenesis. Appearance of more intensive differences at an earlier stage, after 3 months, than after 12 months could be explained by a higher concentration of growth factors in the first period especially PDGF which is responsible for the early phase of wound healing and regeneration as described by Strayhorn *et al*. (1999). The PRP's mechanism of fast regeneration was also described by Camargo *et al*. (2009).

By considering results in a whole, PRP has shown a strong regenerative potential in apexogenesis by bringing preserved pulp vitality and pulp regeneration as a major condition for successful root growth (Holland *et al*., 2008; Trope, 2008) almost completely in the first 3 months. These findings of intensive PRP's effects on pulp regeneration are in correspondence with findings of Torabinejad and Turman (2011). There were not significant differences found between HA and HA+PRP, but it is possible that PRP beneficially acts on periodontal reparation and regeneration (Regan *et al*., 1999; Froum *et al*., 2002; Kim *et al*., 2002; Nakamura *et al*., 2003) thereby reducing the peri-apical reaction.

PRP is an attractive tool in contemporary dentistry and there are results reporting beneficial effects of PRP on the regeneration of dental tissues, but they were usually molecularly evaluated. In our study we investigated both histological and radiological aspects since the radiological signs appear usually later after histological signs, and early positive radiological sings indicate the increased potential of PRP. Radiological evaluation of the method certainly has a significant clinical impact. In our study we did not find any discrepancies between histological and radiological findings, since the dentin bridge was present in both findings in the same percentage. The fact that radiological findings did not differ than those on the molecular level suggest that regenerative processes were intensive so much that the molecular and clinical parameters were on an equal stage.

In our study we did not obtain relevant significance in statistical analyses and that is probably the result of a small sample specific for this type of study, but we certainly found important differences providing the really strong therapeutical potential of PRP in apexogenesis. Further and detailed investigations should be performed on PRP in order to improve it as a part of a standard protocol in treatment of injured pulp in teeth with immature roots.

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EFEKTI PLAZME BOGATE TROMBOCITIMA NA APEKSOGENEZU KOD MLADIH MAJMUNA: RADIOLOŠKA I HISTOLOŠKA EVALUACIJA

PETROVIĆ VANJA, PEJČIĆ NATAŠA, RAKIĆ MIA, LEKOVIĆ V, VASIĆ UNA i STOJIĆ Ž

SADRŽAJ

Primena plazme bogate trombocitima (PRP) predstavlja atraktivnu metodu u savremenoj regenerativnoj medicini zbog toga što ona ima sposobnost da stimuliše proliferaciju i diferencijaciju stem ćelija. Kako su stem ćelije poreklom od dentalne pulpe definisane kao glavne u procesu apeksogeneze, cilj ove studije je bio da radiološki i histološki evaluira efekat PRP na apeksogenezu zuba sa nedovršenim rastom korena. Studija je obuhvatila 8 majmuna (*Cercopithecus Aethiops*) koji su bili podeljeni u dve jednake grupe za evaluiranje, 3 i 12 meseci nakon terapije. Sve životinje su bile podvrgnute istom tretmanu uključujući pulpotomiju i tretman: hidroksiapatitom (HA) – sekutići i HA+PRP – očnjaci. Radiološka evaluacija je urađena određivanjem zadatih parametara na radiogramima dobijenim paralelnom tehnikom dugog konusa, a histološka analiza je sprovedena analiziranjem parametara svojstvenih apeksogenezi u preparatima uzetim "en blok" tehnikom. Dobijeni rezultati su radiološki i histološki za dentinski most posle 3 meseca ukazali na porast u grupi HA+PRP (75%) u poređenju sa HA grupom (50%). Nasuprot tome, posle 12 meseci nije bilo razlike među grupama. Zaostatak u razvoju korena nije utvrđen u HA+PRP grupi za razliku od HA grupe gde je utvrđen zaostatak u 25% slučajeva. Rezultati studije navode na zaključak da je PRP moćno sredstvo za brzu i intezivnu apeksogenezu zbog toga što daje jasne i sveobuhvatne rezultate (najviše u prva tri meseca), koji su radiološki rano vidljivi.