Original Article

Rat Tooth Development Following Local Angiopoietin 1 Application: A Histological Examination

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Abstract

Background: Odontogenesis refers to the process by which teeth originate, erupt, and fuse with the tissues around them. Vascularization that occurs due to angiopoietin 1 (ANGPT1) plays an important role in the development of teeth. **Objectives:** This histological study aimed to elucidate the effects of the local application of ANGPT1 on tooth development in the upper molar area in neonatal rats at different time points. **Materials and Methods:** This study enrolled 24 neonatal rats weighing 3.5–4 g maintained in a controlled environment with respect to temperature and access to food and water. The animals in the experimental group ($n = 12$) were administered 10 µL of ANGPT1 in the upper right molar area, while saline was administered to those in the control group ($n = 12$). The animals were sacrificed on days 3 and 7. The development of the tooth germ area was examined histologically under a light microscope. **Results:** Local application of ANGPT1 protein significantly accelerated the process of tooth development in each of the 12 samples in the experimental group. Early tooth tissue deposition was observed in the experimental group, as evidenced by the increase in the thickness of dentin and enamel, along with an increase in the number of odontoblasts, fibroblasts, and blood vessels, compared with the control group. Statistically significant differences were observed in all variables between the two periods ($P < 0.05$), except for enamel thickness at 3 days ($P = 0.195$). **Conclusion:** Local application of ANGPT1 accelerated tooth development compared with the control group.

Keywords: Angiogenesis, angiopoietin 1, odontogenesis, tooth development

Introduction

Tooth formation is a complex physiological process characterized by bud, cap, and bell stages. This process entails a series of molecular interactions between the odontogenic epithelium and neural crest-derived ectomesenchymal cells.[1]

Teeth develop from the ectoderm and ectomesenchyme. Enamel is produced by a structure known as the enamel organ, which is derived from the primordial oral epithelium that lines the stomodeum (primitive oral cavity). Tooth development, including the differentiation of the formative cells of the tooth and the timing of their secretion, is guided by epithelial–mesenchymal interactions. The dental papilla develops from ectomesenchymal cells located near the inner margins of the enamel organ to form dentin and pulp, while the ectomesenchymal cells located near the outer margins constitute the dental follicle that is responsible for the formation of the cementum, periodontal ligament, and alveolar bone.[2]

Tooth development commences via the formation of epithelial bands that form two ingrowths called dental lamina (located lingually) and vestibular lamina (buccally positioned). These ingrowths extend into the mesenchyme. The vestibular lamina proliferates within the mesenchyme, which results in the development of the vestibule (between the cheek and tooth-bearing portion of the jaw). The dental lamina generates epithelial outgrowths towards the mesenchyme, corresponding to the future position of the deciduous teeth.[3]

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The dental papilla arises from the ectomesenchyme and develops into a pulp after becoming encased in mineralized tissue. The two structures are enveloped by the dental follicle.[4]

It is hypothesized that epithelial–mesenchymal interactions at the level of individual teeth and vascular endothelial growth factor signaling at the level of the teeth as a target regulate the development of the tooth's vascular supply.[5]

The subodontoblastic region has a blood vessel plexus, which is visible in the dental pulp. Moreover, some blood vessels appeared to have progressed to the odontoblast layer. The number of blood vessels in the tooth's epithelial compartment had risen. They are situated next to the stratum intermedium cells near the ameloblast layer, forming a plexus-like structure.[5]

Regeneration of pulp tissue following injury depends on the early establishment of a local microvascular network that supplies the cells with oxygen and nutrients. Well-coordinated angiogenic signaling processes are required to develop the complex network of blood vessels in the tooth pulp.[6]

Angiopoietin 1 (ANGPT1), an oligomeric glycoprotein, is a member of the angiopoietin family of growth factors, including ANGPT2 and ANGPT3/4. These ligands interact with TIE2, one of the tyrosine kinases belonging to the tyrosine kinase (TIE) family of receptors. The other receptor, TIE1, is primarily expressed in the vascular endothelium. The principal roles of angiopoietin and the TIE family include the regulation of vessel remodeling and stabilization in the adult vasculature and the later stages of vascular development. ANGPT1 promotes the structural integrity of adult vasculature and is necessary for the proper organization and maturation of newly formed capillaries. The significance of ANGPT1 in the development of angiogenesis has been demonstrated in ligand-deficient transgenic mice.[7]

The expression levels of hypoxia-inducible factor 1, ANGPT1, ANGPT2, and TIE2 were considerably higher in the complete root development group than in the incomplete root development group.[8]

In experimental animal models, angiogenesis has been demonstrated to be essential for effective tumor growth, invasion, and metastasis.[9] The general structure of angiopoietins is similar, consisting of a short amino-terminal motif, a coiled-coil domain, and a fibrinogen-like domain at the carboxy terminus.[10] ANGPT1 exerts strong vascular protective actions by reducing plasma leakage, ameliorating vascular inflammation, and preventing endothelial death. Preclinical research suggests that the therapeutic use of ANGPT1 may be beneficial for edema, endotoxemia, and transplant arteriosclerosis.[11]

One study found that upregulating ANGPT1 reduced cerebral infarction size,[12] and this was supported by a meta-analysis in which Ang1 might be a promising target molecule for developing vasoprotective therapies for controlling hemorrhagic transformation and cerebral edema after tissue plasminogen activator treatment.[13]

ANGPT1/2 might have a central role in pneumonia-induced inflammation and permeability due to its strong vascular protective features. Higher levels of ANGPT2 in the blood predicted death and length of hospital stay, and ANGPT1 may be a therapeutic target for severe pneumonia.[14]

One important pathway in angiogenesis is the angiopoietin-TIE system. A TIE-2 receptor agonist called ANGPT1 is believed to have stabilizing and anti-inflammatory actions on the endothelium. While ANGPT2 is elevated before the disease starts, and that increase reflects disease severity, this suggests that ANGPT2 may have a role in the pathophysiology of heart failure.[15] As well as the absence of the ANGPT1/tyrosine kinase vascular growth factor system, metastasis increases without impacting initial tumor development.[16]

Therefore, this animal study aimed to elucidate the effects of local application of ANGPT1 on tooth development in the upper molar area in neonatal rats at different time points.

Materials and Methods

This study employed 24 neonatal rats (on their first day after birth) weighing 3.5–4 g, which were maintained under a controlled environment with respect to temperature and access to food and water. The animals were administered 10 µL of ANGPT1 (from MyBioSource Co., San Diego, California, United States) at a concentration of 0.03 mg/mL in deionized water in the upper right molar area [Figure 1]. The rats were sacrificed on days 3 and 7. The development of the molar tooth germ area was investigated histologically using sagittal sections obtained from the decapitated head of the neonatal rat. The specimens were processed and stained with hematoxylin and eosin before examination under a light microscope.

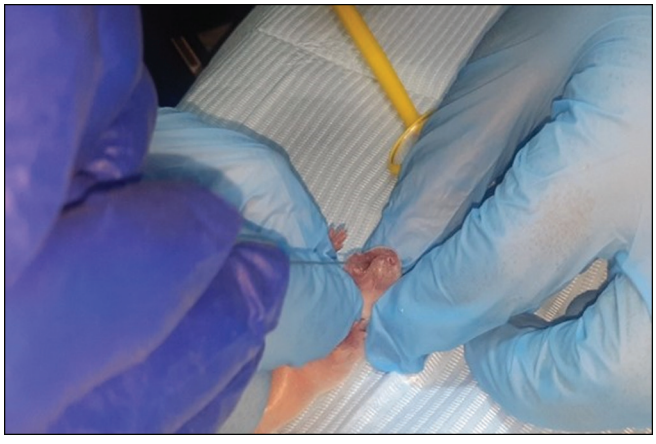

Figure 1: Local administration of ANGPT1

Measurement of dentin and enamel thickness was performed by a subjective method using double-blind examination (interexamination and intraexamination) by using (imageJ. exe) program in four represented microscopical fields at ×40 magnification by measuring the distance between enamel and odontoblasts cell layer in both examination and control group in two periods—3 and 7 days.[17,18]

Assessed vascular development in different areas of the pulp in four represented microscopic fields at ×40 magnification in both examination and control groups in two periods—3 and 7 days.[5]

Surgical procedure

All surgical and nonsurgical procedures were performed in a sterile environment under humane conditions. The right molar regions of 12 rats were selected for daily injection of exogenous ANGPT1 (10 µL) into the jawbone of the maxillary molar (experimental group). The other 12 rats were administered normal saline (control group). The rats were sacrificed on days 3 and 7 using the appropriate and humane procedures; six rats from each group were euthanized at designated time points.

On postnatal days 3 and 7, a 31-gauge needle was inserted into the raised bulge that approximated the location of the beneath first molar tooth germ at an angle of 45° using manual force.[19] However, the enamel organ was not pierced.

Histological specimen preparation

The tooth and bone specimens were fixed for 24 h in 10% freshly prepared formalin. Thereafter, the specimens were immersed in 10% formic acid to initiate the decalcification process, which lasted for 1–2 h. The decalcification process was checked using a small needle, which penetrated the bone deeply when decalcification was completed.

A segment of 4–5 µm sectioned from the wax block of the sample in the regular architecture, which was stained with hematoxylin and eosin. A light magnification lens was used for the histological evaluation.

Statistical analysis

Statistical analysis was performed using Statical Package of Social Sciences (SPSS, IBM, Chicago, Illinois, United States) 26. Independent sample *t*-test was used to compare enamel and dentin thickness, as well as the number of blood vessels and pulp tissue cells of all groups. Also, the results were expressed as the mean, minimum, maximum, standard deviation, standard error, and *P*-value.

Ethical approval

All experiments were conducted in accordance with the ethical guidelines of the College of Dentistry, University of Baghdad (Reference number: 463).

Results

In the control group, histological examination of tooth germ of the upper first molar at postnatal day 3 at bell stage revealed a layer of dentin close to the odontoblastic layer and an enamel layer approximating the ameloblastic layer in the coronal and cervical areas of the tooth [Figure 2A and B; Tables 1 and 2].

On day 7, a histological examination of the same tooth showed well-polarized ameloblasts between the enamel layer and stratum intermedium and a layer of predentin in proximity to the odontoblastic layer, which was located under a layer of dentin in the coronal and cervical areas of the tooth [Figure 2C and D; Tables 1 and 2].

In the experimental group, the enamel thickness increased at 3 days, although without statistical significance. Ameloblasts were observed adjacent to the enamel. The thickness of the dentin was also increased close to the odontoblastic layer [Figure 3A and B; Tables 1 and 2].

On day 7, the increase in the thickness of enamel and dentin was statistically significant and accompanied by the presence of a layer of ameloblasts and odontoblasts [Figure 3C and D; Tables 1 and 2].

Also showed an increased number of blood vessels in the pulp [Figure 4A and B].

In addition, you can compare the histological view of 3 days [Figure 4C] and 7 days [Figure 4D] at magnification power ×40, showing all tooth sections and demonstrating ameloblasts, enamel, dentin, and odontoblasts in a secretory stage.

Histological analysis

The enamel and dentin thickness was measured histologically and are expressed as the minimum, mean, maximum, standard deviation, standard error, and *P*-values for the two time points (days 3 and 7). The experimental group exhibited an increase in the thickness of enamel and dentin in both periods compared with the control group [Tables 1 and 2].

The cellular components of the pulp tissue and the number of blood vessels were measured histologically and are presented as the minimum, mean, maximum, standard deviation, standard error, and *P*-value for the two time points (days 3 and 7). The experimental group exhibited increased pulp tissue cells and blood vessels in both periods compared with the control group [Table 3].

Discussion

This study evaluated the effect of the local application of ANGPT1 to the upper molar area during tooth formation due to its angiogenic potential. We found that the thickness of enamel and dentin had increased

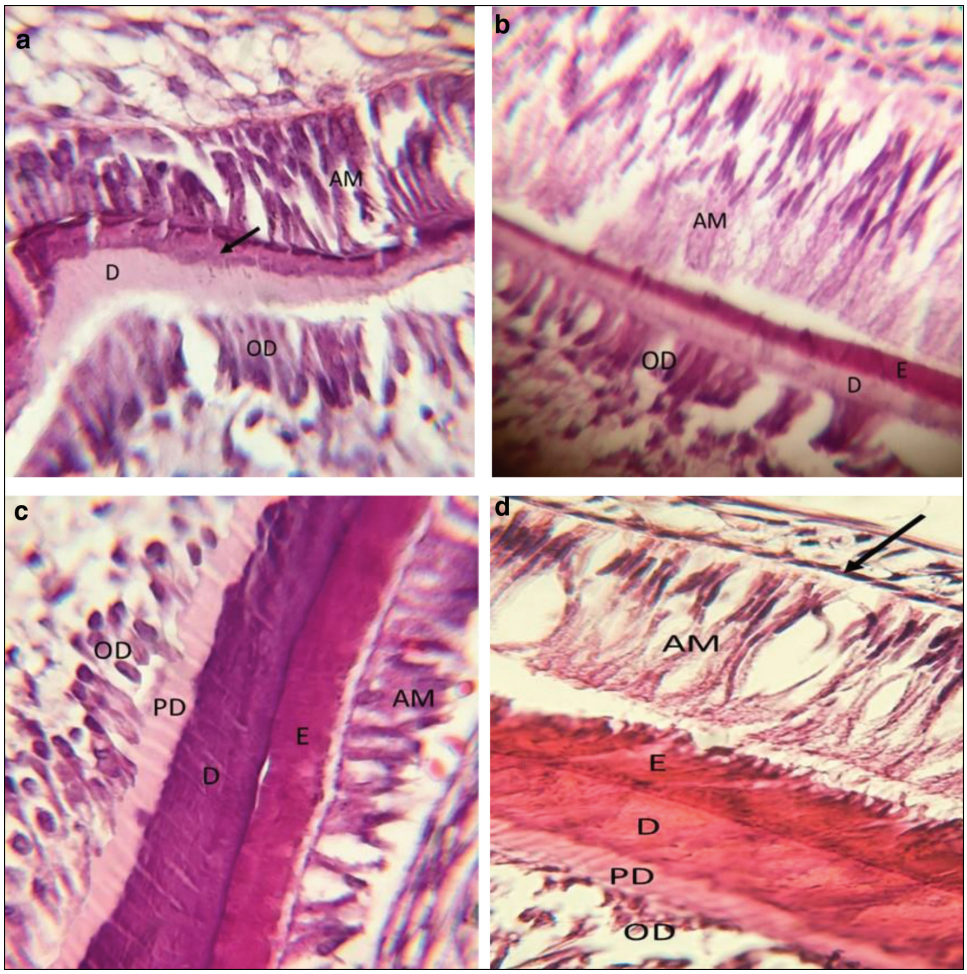

Figure 2: (a) Histological view of the occlusal area of the control group at three days showing ameloblasts (AM), enamel matrix (arrow), dentin (D), and odontoblasts (OD), hematoxylin and eosin ×400. (b) Histological view of the cervical area at three days in the control group showing ameloblasts (AM), enamel matrix (E), dentin (D), and odontoblasts (OD), hematoxylin and eosin ×400. (c) Histological view of the cervical area at seven days in the control group showing ameloblasts (AM), enamel matrix (E), dentin (D), predentin (PD), and odontoblasts (OD), hematoxylin and eosin ×400. (d) Histological view of the area near the cusp tip at seven days in the control group showing ameloblasts (AM), enamel matrix (E), dentin (D), odontoblasts (OD), predentin (PD), and stratum intermedium (black arrow), hematoxylin and eosin ×400

Table 1: Descriptive statistics of enamel thickness (hematoxylin and eosin) in the control and experimental groups at both time periods

Duration	Group	Descriptive statistics					Comparison	
		Mean (μm)	S.D.	Min.	Max.	S.E.	*t*-Test	*P*-value
3 days	Control	124.922	17.519	93.994	145.210	7.152	−1.390	0.195
	Angiopoietin 1	144.544	29.800	89.218	174.105	12.166		
7 days	Control	132.557	21.429	108.372	161.696	8.748	−5.239	0.000*
	Angiopoietin 1	183.005	9.862	166.074	193.941	4.026		

*Significant at $P < 0.05$

in the upper molar area after 3 and 7 days. Additionally, microscopic examination demonstrated new blood vessel formation in the pulpal area with increased odontoblasts and fibroblasts [Figure 4A and B].

The increase in enamel thickness at 3 days in the experimental group did not differ significantly from that in the control group. Our results coincide with those of a previous study that investigated the offspring of rats with gestational diabetes mellitus.[18]

In contrast to enamel thickness, we found that dentin thickness was higher in the experimental group than in the control group. This finding coincides with a study

Table 2: Descriptive statistics of dentin thickness (hematoxylin and eosin) in the control and experimental group for both time periods

Duration	Group	Descriptive statistics					Comparison	
		Mean (μm)	S.D.	Min.	Max.	S.E.	*t*-Test	*P*-value
3 days	Control	149.670	18.153	117.065	163.113	7.410	−2.487	0.032*
	Angiopoietin 1	181.458	25.508	132.085	204.275	10.413		
7 days	Control	155.572	15.230	137.893	176.525	6.217	−4.687	0.004*
	Angiopoietin 1	185.778	4.154	181.163	192.107	1.695		

*Significant at $P < 0.05$

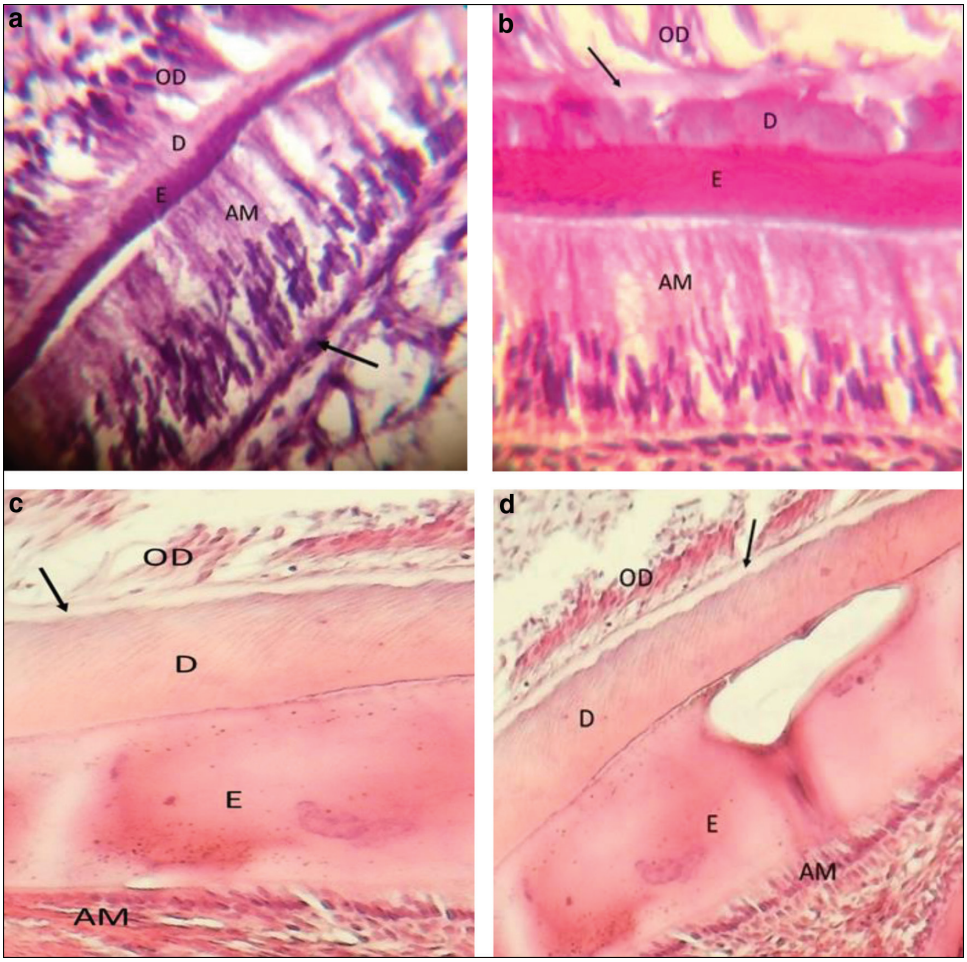

Figure 3: (a) Histological view of the cervical area at three days in the experimental group showing ameloblasts (AM), enamel matrix (E), dentin (D), odontoblasts (OD), and stratum intermedium (black arrow), hematoxylin and eosin ×400. (b) Histological view of the area near the cusp tip in the experimental group at three days showing ameloblasts (AM), enamel matrix (E), dentin (D), odontoblasts (OD), and predentin (black arrow), hematoxylin and eosin ×400. (c) Histological view of the experimental group at seven days showing ameloblasts (AM), enamel matrix (E), dentin (D), odontoblasts (OD), and predentin (black arrow), hematoxylin and eosin ×400. (d) Histological view of the experimental group at seven days showing ameloblasts (AM), enamel matrix (E), dentin (D), predentin (black arrow), and odontoblasts (OD), hematoxylin and eosin ×400

that investigated the effect of leptin on odontoblastic differentiation and angiogenesis.[20]

In addition, the increase in the number of blood vessels and pulpal tissue cells (odontoblasts, endothelial cells, and fibroblasts) observed in this study is in agreement with a previous study that focused on bone repair, which observed the formation of osteoid tissue filling the bony defect with newly formed blood vessels.[21]

At 7 days, a significant increase in the thickness of enamel was noted in the experimental group compared with the control group. Our result coincides with a study that measured the secretory zone of enamel at different durations.[22]

We found an increase in dentin thickness in the experimental group, which was greater than that in the control group. This result coincides with a study done

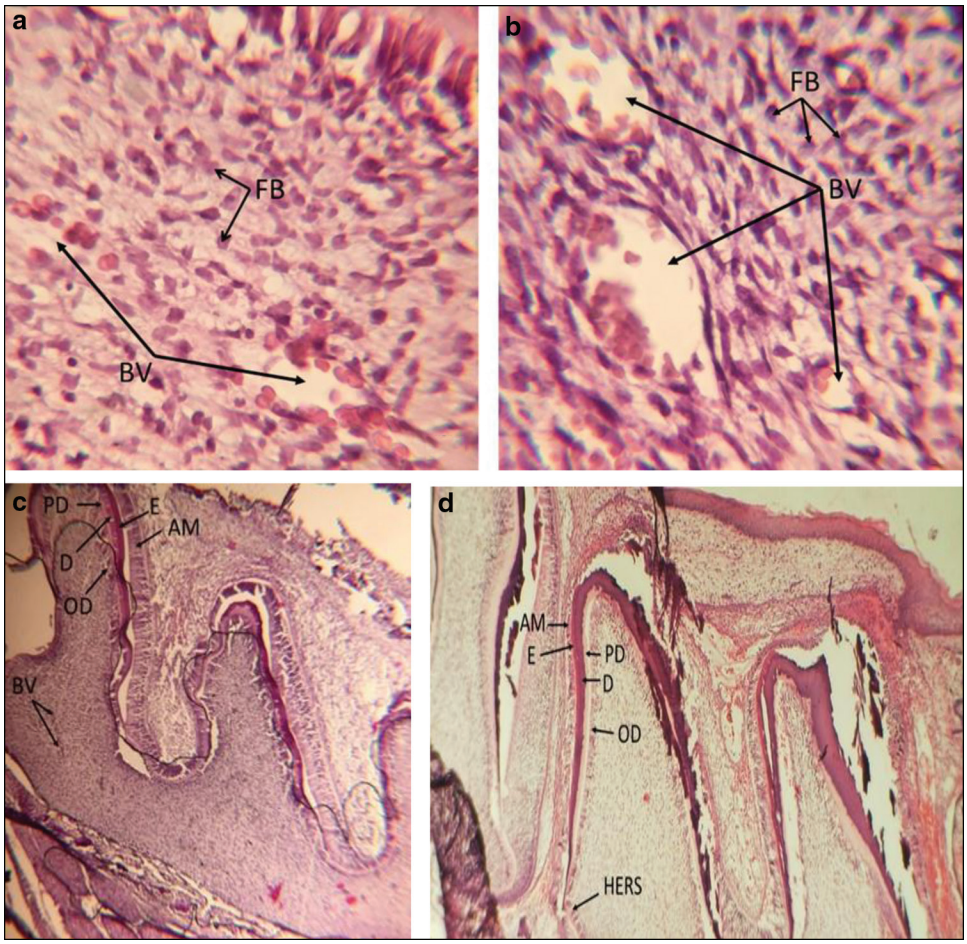

Figure 4: (a and b) Histological view of the experimental group at seven days showing fibroblasts (FB), odontoblasts (OD), and blood vessels (BV), hematoxylin and eosin ×40. (c) Histological view at three days showing ameloblasts (AM), enamel matrix (E), dentin (D), predentin (PD), odontoblasts (OD), and blood vessels (BV), hematoxylin and eosin ×40. (d) Histological view at seven days showing ameloblasts (AM), enamel matrix (E), dentin (D), predentin (PD), odontoblasts (OD), and Hertwig's Epithelial Root Sheath (HERS), hematoxylin and eosin ×40

Table 3: Descriptive statistics of pulp tissue cells with blood vessels (hematoxylin and eosin) in the control and experimental group at both time periods

Variables	Duration	Group	Descriptive statistics					Comparison	
			Mean cell count	S.D.	Min.	Max.	S.E.	*t*-Test	*P*-value
Pulp tissue cell	Day 3	Control	199.574	25.473	174.333	246.361	10.399	−4.003	0.003*
		Angiopoietin 1	284.731	45.459	229.500	360.611	18.558		
	Day 7	Control	253.745	20.930	212.388	269.972	8.544	−4.756	0.001*
		Angiopoietin 1	346.185	42.759	276.833	394.888	17.456		
Blood vessels	Day 3	Control	12.777	3.987	7.666	19.000	1.627	−4.879	0.002*
		Angiopoietin 1	30.500	7.954	20.333	39.666	3.247		
	Day 7	Control	16.500	7.332	6.666	24.000	2.993	−3.836	0.003*
		Angiopoietin 1	32.111	6.751	20.666	38.000	2.756		

*Significant at $P < 0.05$

that measured the predentin thickness, which is eventually converted to mature dentin.[5]

Furthermore, the number of blood vessels and pulp tissue cells (odontoblasts, endothelial cells, and fibroblasts) increases, which is in agreement with a study that discovered that the development and orientation of pulpal blood vessels occur in a discrete, spatiotemporally regulated manner, which is intricately linked to tooth morphogenesis and cell differentiation.[17]

The findings of this research on the effect of local application of ANGPT1 on tooth development in rats demonstrate significant clinical implications. The study

suggests that using ANGPT1 can accelerate tooth development by increasing the thickness of enamel and dentin and promoting the growth of blood vessels. This is an important finding because delayed tooth development can lead to various dental abnormalities and defects. By decreasing the occurrence of such abnormalities and defects, ANGPT1 can improve the overall health of teeth. Furthermore, the research indicates that the application of ANGPT1 can also benefit the eruption of teeth. This can lead to improved oral health outcomes, particularly in individuals with delayed tooth eruption.

This research on the effect of local application of ANGPT1 on tooth development in rats makes an important contribution to the existing literature. The study indicates that the use of ANGPT1 can accelerate tooth development, potentially leading to a decrease in the number of extracted teeth due to the effect ANGPT1 on the proliferation of blood vessels that supply the nutrition to the ameloblast and odontoblast as well as pulp tissue cells, which are important to form a healthy tooth and reduce the need to be extracted. This is a crucial finding because extracted teeth can cause a variety of dental and systemic health complications. Additionally, the study suggests that ANGPT1 may be beneficial in reducing tooth crowding and its associated complications, in view of the fact that ANGPT1 maintains well-erupted and developed teeth. This finding can have important implications for orthodontic treatments, as tooth crowding is a common issue that often requires intervention.

Furthermore, the research provides a unique insight into the effects of ANGPT1 on tooth development. While previous studies have explored the role of ANGPT1 in vascular development and wound healing, this study specifically focuses on its effects on dental development. By demonstrating the potential benefits of ANGPT1 on tooth development, this research expands our understanding of the molecule's broader biological functions.

While this research on the effect of local application of ANGPT1 on tooth development in rats provides valuable insights, there are some limitations that should be considered. The site of injection can have an impact on the tooth germ and may result in issues during sample preparation for histological evaluation. In this study, the injection was performed directly into the tooth germ, which may have led to the destruction of some parts of the germ. This limitation could affect the accuracy of the histological view of the samples, potentially resulting in inaccurate findings. Future studies could explore alternative injection techniques that minimize the potential damage to the tooth germ.

This limitation is that the injection technique used in this study may not be the optimal method for delivering ANGPT1 to the tooth germ. The study used an injection technique that was performed directly into the tooth germ, which may not be practical for clinical use. Infiltration technique in the sulcus of the jaw adjacent to the tooth germ might be more suitable for clinical applications. Thus, further research could explore the effectiveness of different delivery methods for ANGPT1 in promoting tooth development.

Given the limitations of this study on the effect of local application of ANGPT1 on tooth development in rats, future research could explore alternative administration methods. Rather than directly local application, future studies could investigate the effectiveness of systemic or topical administration of ANGPT1 in promoting tooth development. Systemic administration could involve injecting ANGPT1 into the bloodstream or oral cavity, while topical administration could involve applying it directly to the surface of the tooth or gums. These alternative methods could provide more practical and clinically relevant approaches for delivering ANGPT1 to the tooth germ.

Furthermore, while this study provides valuable preclinical data on the potential benefits of ANGPT1 in dental development, further research is needed to confirm these findings. Future studies could investigate the effectiveness of ANGPT1 in promoting tooth development in other animal models or in human subjects. Additionally, studies could explore the optimal dose, frequency, and duration of ANGPT1 administration for dental development.

Conclusion

Local administration of the ANGPT1 protein accelerated tooth formation compared to the control group by increasing dentin and enamel thickness due to an increase in the number of odontoblasts, fibroblasts, and blood vessels.

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Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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