Simvastatin Loaded Chitosan-Plga Nano Hydrogel Scaffold for Regenerative Endodontics: A Randomised Controlled Trial

Dr. Vanshika Agarwal[1], Dr. Gaurav Patri[2*], Dr. Raina Rastogi[3], Dr. Vishwas L[4], Dr. Ananya Sharma[5], Dr. Yashika Soni[6]

[1] Post Graduate Trainee, Kalinga Institute of Dental Sciences, KIIT Deemed to be University, Bhubaneswar, Odisha, India.
[2*] Professor, Kalinga Institute of Dental Sciences, KIIT Deemed to be University, Bhubaneswar, Odisha, India.
(Corresponding Author) Email: patrigaurav@gmail.com
[3] Kothiwal Dental College and Research Centre, Mora Mustaqeem, Moradabad, Uttar Pradesh, India.
[4] Post Graduate Student, Sri Rajiv Gandhi College of Dental Sciences and Hospital, Bangalore, Karnataka, India.
[5] PG Third Year, ITS Dental College, Greater Noida - 201306, Uttar Pradesh, India.
[6] PG Second Year, ITS Dental College, Greater Noida - 201306, Uttar Pradesh, India.

Received: 20th Feb, 2026 | **Revised:** 4th Mar, 2026 | **Accepted:** 25th Mar, 2026 | **Available Online:** 10th Apr, 2026

ABSTRACT

Background: Regenerative endodontics aims to restore the vitality and function of the pulp–dentin complex in immature necrotic teeth. Conventional approaches relying on blood clot scaffolds have shown clinical success but often yield limited regenerative outcomes. Recent advances in biomaterials and drug delivery systems have introduced bioactive scaffolds, such as simvastatin-loaded chitosan–PLGA nano hydrogels, which may enhance tissue regeneration through sustained release and biological modulation.

Aim: To evaluate and compare the clinical and radiographic outcomes of a simvastatin-loaded chitosan–PLGA nano hydrogel scaffold with a conventional blood clot scaffold in regenerative endodontic procedures.

Materials and Methods: This randomized controlled trial included 40 patients aged 8–16 years with immature permanent teeth exhibiting pulp necrosis and open apices. Participants were randomly allocated into two groups: Group I (experimental) received a simvastatin-loaded chitosan–PLGA nano hydrogel scaffold, while Group II (control) was treated using a conventional blood clot scaffold. Standard regenerative endodontic protocols were followed in both groups. Clinical and radiographic evaluations were conducted at baseline, 3, 6, and 12 months. Parameters assessed included pain, swelling, sinus tract, root lengthening, apical closure, and dentinal wall thickness. Statistical analysis was performed using appropriate tests with a significance level set at $p < 0.05$.

Results: Out of 40 patients, 36 completed the study. Both groups demonstrated comparable clinical success with resolution of symptoms ($p > 0.05$). However, the experimental group showed significantly greater radiographic improvement in root length ($p = 0.01$), dentinal wall thickness ($p = 0.002$), and apical closure ($p = 0.001$) at 12 months compared to the control group. These findings indicate enhanced regenerative potential with the simvastatin-loaded scaffold.

Conclusion: The use of a simvastatin-loaded chitosan–PLGA nano hydrogel scaffold significantly improves radiographic outcomes in regenerative endodontics while maintaining comparable clinical success to conventional methods. This approach represents a promising advancement in biologically driven endodontic therapy.

Keywords: Chitosan, Nano hydrogel, Regenerative endodontics, Simvastatin, Tissue engineering.

How to cite this article: Agarwal V, Patri G, Rastogi R, Vishwas L, Sharma A, Soni Y. Simvastatin Loaded Chitosan-Plga Nano Hydrogel Scaffold for Regenerative Endodontics: A Randomised Controlled Trial. Int J Drug Deliv Technol. 2026;16(32s):290-295. DOI: 10.25258/ijddt.16.32s.35

Source of support: Nil.

Conflict of interest: The authors declare no conflict of interest.

Introduction

Regenerative endodontics has emerged as a paradigm shift in the management of immature permanent teeth with necrotic pulps, aiming not merely at disinfection and obturation but at the restoration of pulp–dentin complex vitality and continued root development [1]. Conventional endodontic procedures, although highly successful in eliminating infection, fail to re-establish the biological functions of the pulp tissue, often resulting in structurally compromised teeth with thin dentinal walls and increased susceptibility to fracture. In this context, regenerative endodontic procedures (REPs) seek to harness the principles of tissue engineering—namely stem cells, growth factors, and scaffolds—to promote true biological regeneration within the root canal system [2].

A critical component of successful regeneration is the scaffold, which provides a three-dimensional microenvironment conducive to cell adhesion, proliferation, and differentiation. Among the various biomaterials explored, chitosan and poly(lactic-co-glycolic acid) (PLGA) have gained considerable attention due to their biocompatibility, biodegradability, and favorable physicochemical properties [3]. Chitosan, a naturally derived polysaccharide, exhibits intrinsic antimicrobial activity and promotes wound healing, while PLGA, a synthetic copolymer, allows for controlled drug release and structural stability. The integration of these materials into a nano hydrogel scaffold offers an advanced platform capable of mimicking the extracellular matrix and facilitating sustained delivery of bioactive molecules [4].

Recent research has highlighted the potential of statins, particularly simvastatin, as bioactive agents in regenerative dentistry. Beyond their well-known lipid-lowering effects, statins possess pleiotropic properties including anti-inflammatory, angiogenic, and osteogenic effects. Simvastatin has been shown to enhance the expression of bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), and other signaling molecules essential for tissue regeneration. Its incorporation into a nano hydrogel scaffold enables localized, controlled release within the root canal system, thereby maximizing its therapeutic efficacy while minimizing systemic exposure [5,6].

Despite promising in vitro and preclinical findings, there remains a paucity of high-quality clinical evidence evaluating the efficacy of simvastatin-loaded scaffolds in regenerative endodontics. Randomized controlled trials are essential to validate their clinical applicability, assess treatment outcomes such as root lengthening, apical closure, and dentinal wall thickening, and compare their performance with conventional regenerative protocols [7,8]. Additionally, factors such as scaffold degradation rate, drug release kinetics, and host response need to be systematically investigated to optimize treatment protocols [9,10].

Therefore, the present randomized controlled trial aims to evaluate the clinical and radiographic outcomes of a simvastatin-loaded chitosan-PLGA nano hydrogel scaffold in regenerative endodontic procedures. By integrating advanced biomaterials with pharmacological modulation, this study seeks to contribute to the evolving landscape of biologically driven endodontic therapies and establish evidence-based strategies for enhancing regenerative outcomes.

Methodology

This study was designed as a parallel-group, randomized controlled clinical trial to evaluate the efficacy of a simvastatin-loaded chitosan–PLGA nano hydrogel scaffold in regenerative endodontic procedures. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants or their guardians prior to enrollment. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

A total of patients aged 8–16 years presenting with immature permanent teeth diagnosed with pulp necrosis and open apices were recruited from the outpatient department. Teeth exhibiting periapical radiolucency, absence of root development, and clinical signs such as discoloration or sinus tract were included. Teeth with root fractures, advanced periodontal disease, or systemic conditions affecting healing were excluded. The sample size was determined based on prior pilot data, ensuring adequate statistical power.

Participants were randomly allocated into two groups using a computer-generated randomization sequence. Group I (experimental group) received regenerative endodontic treatment using a simvastatin-loaded chitosan–PLGA nano hydrogel scaffold, while Group II (control group) underwent conventional regenerative endodontic procedures using a blood clot scaffold. Allocation concealment was ensured using sealed opaque envelopes.

All procedures were performed under local anesthesia and rubber dam isolation. In the first appointment, access cavity preparation was carried out, followed by minimal or no instrumentation of the root canal walls to preserve stem cell viability. The canals were gently irrigated using 1.5% sodium hypochlorite, followed by saline and 17% EDTA to remove the smear layer and expose dentinal tubules. The canals were then dried with sterile paper points, and an intracanal medicament (calcium hydroxide) was placed. The access cavity was sealed temporarily, and patients were recalled after 2–3 weeks.

At the second visit, if the tooth was asymptomatic, the intracanal medicament was removed using saline irrigation. In the control group, bleeding was induced into the canal by over-instrumentation beyond the apex to create a natural blood clot scaffold. In the experimental group, the prepared simvastatin-loaded chitosan–PLGA nano hydrogel scaffold was introduced into the canal space up to the level of the cementoenamel junction. The nano hydrogel was synthesized using an emulsion-solvent evaporation technique for PLGA nanoparticles, followed by incorporation into a chitosan-based hydrogel matrix, ensuring controlled drug release and structural integrity.

In both groups, a collagen matrix was placed over the scaffold, followed by the application of mineral trioxide aggregate (MTA) as a coronal barrier. The access cavity was subsequently restored with a permanent restorative material.

Clinical and radiographic evaluations were performed at baseline, 3 months, 6 months, and 12 months. Clinical parameters included pain, swelling, sinus tract, and tooth mobility. Radiographic assessment was carried out using standardized periapical radiographs to evaluate root lengthening, apical closure, and dentinal wall thickening. All radiographic measurements were analyzed using digital imaging software by blinded evaluators.

Data were statistically analyzed using appropriate software. Continuous variables were expressed as mean ± standard deviation, and intergroup comparisons were performed using independent t-tests or Mann–Whitney U tests as applicable. Intragroup comparisons over time were analyzed using repeated measures ANOVA. A p-value of <0.05 was considered statistically significant.

This methodological framework was designed to ensure reproducibility, minimize bias, and provide robust clinical evidence regarding the effectiveness of the simvastatin-loaded nano hydrogel scaffold in regenerative endodontics.

Results

A total of 40 patients were initially enrolled in the study, of which 36 patients (n = 18 in each group) completed the 12-month follow-up period. Four participants were lost to follow-up due to non-compliance. Both groups were comparable at baseline with respect to age, gender distribution, and preoperative clinical and radiographic characteristics, with no statistically significant differences ($p > 0.05$), ensuring homogeneity between the study cohorts.

At the 3-month follow-up, both groups demonstrated satisfactory resolution of clinical signs and symptoms, including pain, swelling, and sinus tract formation. However, the experimental group (simvastatin-loaded scaffold) showed a slightly higher rate of early symptomatic relief, although the difference was not statistically significant ($p > 0.05$). By 6 and 12 months, complete clinical success was observed in the majority of cases in both groups, with no significant intergroup difference in terms of pain or infection control.

Radiographic evaluation revealed progressive healing in both groups; however, the experimental group exhibited significantly greater improvement in parameters associated with regeneration. Increased root length, enhanced apical closure, and significant dentinal wall thickening were more pronounced in the simvastatin group at both 6 and 12 months. These findings indicate the beneficial role of simvastatin in promoting hard tissue formation and continued root development.

Quantitative analysis demonstrated that the mean increase in root length and dentinal wall thickness was significantly higher in the experimental group compared to the control group at the 12-month interval ($p < 0.05$). Similarly, the reduction in apical diameter, indicative of apical closure, was significantly greater in the experimental group. These outcomes suggest that the nano hydrogel scaffold facilitated sustained drug release and enhanced regenerative potential within the root canal system.

Table 1: Baseline Characteristics of Study Participants

Parameter	**Group I (Experimental) (n=18)**	**Group II (Control) (n=18)**	**p-value**

Mean Age (years)	12.4 ± 2.1	12.1 ± 2.3	0.68
Male/Female	10/8	9/9	0.73
Teeth Type (Anterior/Posterior)	12/6	11/7	0.71
Presence of Sinus Tract (n, %)	6 (33.3%)	7 (38.8%)	0.72

No statistically significant difference was observed between groups at baseline (Table 1).

Table 2: Clinical Outcomes at Follow-Up Intervals

Time Interval	**Group I (n=18) – Success n (%)**	**Group II (n=18) – Success n (%)**	**p-value**
3 Months	16 (88.9%)	15 (83.3%)	0.63
6 Months	17 (94.4%)	16 (88.9%)	0.54
12 Months	18 (100%)	17 (94.4%)	0.31

Clinical success was comparable between groups across all intervals (Table 2).

Table 3: Radiographic Changes in Root Length (mm)

Time Interval	**Group I (Mean ± SD)**	**Group II (Mean ± SD)**	**p-value**
Baseline	10.2 ± 1.3	10.4 ± 1.2	0.59
6 Months	11.8 ± 1.4	11.1 ± 1.3	0.04*
12 Months	13.1 ± 1.5	11.9 ± 1.4	0.01*

Statistically significant increase in root length in Group I at 6 and 12 months (Table 3).

Table 4: Radiographic Evaluation of Dentinal Wall Thickness and Apical Closure

Parameter	**Group I (Mean ± SD)**	**Group II (Mean ± SD)**	**p-value**
Dentinal Wall Thickness (12 months)	1.8 ± 0.3 mm	1.3 ± 0.2 mm	0.002*
Apical Diameter Reduction (%)	72.5 ± 8.4	54.2 ± 7.9	0.001*

Group I showed significantly better dentinal thickening and apical closure (Table 4).

Overall, the findings of this randomized controlled trial demonstrate that the incorporation of simvastatin into a chitosan–PLGA nano hydrogel scaffold significantly enhances radiographic outcomes associated with regenerative endodontics, while maintaining comparable clinical success rates to conventional approaches.

Discussion

The findings of the present randomized controlled trial demonstrate that the incorporation of a simvastatin-loaded chitosan–PLGA nano hydrogel scaffold significantly enhances radiographic outcomes in regenerative endodontics when compared to the conventional blood clot scaffold. Although both groups achieved comparable clinical success in terms of infection resolution and absence of symptoms, the experimental group showed superior outcomes in root lengthening, apical closure, and dentinal wall thickening, indicating a more favorable regenerative response.

The improved regenerative outcomes observed in this study can be attributed to the synergistic effects of simvastatin and the chitosan–PLGA scaffold system. Simvastatin is known to exert pleiotropic effects beyond its lipid-lowering action, including promotion of angiogenesis, osteogenesis, and anti-inflammatory activity. Soares et al. [13] demonstrated that simvastatin-releasing chitosan scaffolds significantly enhance pulp–dentin regeneration by stimulating odontoblastic differentiation and mineralized tissue formation. This is consistent with the present findings, where increased dentinal wall thickness and apical closure were evident in the experimental group.

The role of chitosan as a scaffold material is also critical in achieving these outcomes. Chitosan possesses excellent biocompatibility, biodegradability, and intrinsic antimicrobial properties, making it highly suitable for endodontic applications. Atia et al. [14] reported that drug-loaded chitosan scaffolds provide a conducive microenvironment for cellular proliferation and differentiation, thereby enhancing tissue regeneration. Additionally, the incorporation of PLGA enables controlled and sustained drug release, which is essential for maintaining therapeutic concentrations of simvastatin within the root canal system over time.

The significance of nanoparticle-based delivery systems has been increasingly recognized in regenerative dentistry. Chang et al. [11] developed core-shell PLGA–chitosan nanospheres loaded with simvastatin and doxycycline, demonstrating enhanced periodontal and osseous repair through controlled drug delivery and improved tissue response. Similarly, Alzahrani et al. [10] highlighted the effectiveness of chitosan-functionalized nanoparticles in delivering bioactive agents, resulting in modulation of inflammatory markers and gene expression. These findings support the concept that nano-engineered scaffolds can significantly improve the biological performance of regenerative materials.

Furthermore, the importance of scaffold architecture and biomaterial design in regenerative endodontics has been emphasized by Liu et al. [15], who noted that scaffolds mimicking the extracellular matrix and enabling sustained release of bioactive molecules are crucial for successful tissue regeneration. The nano hydrogel scaffold used in the present study likely provided a three-dimensional framework that facilitated stem cell migration, attachment, and differentiation, thereby contributing to enhanced regenerative outcomes.

In addition to clinical implications, recent advancements in chitosan-based technologies have broadened their applications in dentistry. Sinha et al. [12] discussed the versatility of chitosan in various dental innovations, highlighting its potential in both therapeutic and environmental applications. This underscores the adaptability of chitosan as a biomaterial and supports its continued exploration in regenerative endodontics.

Despite the promising results, certain limitations must be acknowledged. The sample size was relatively limited, and the follow-up period was restricted to 12 months, which may not fully reflect long-term clinical performance. Moreover, histological validation of true pulp–dentin complex regeneration was not feasible. Future studies incorporating larger cohorts, extended follow-up, and advanced imaging or molecular analyses are recommended to further substantiate these findings.

Conclusion

In summary, the present study reinforces the potential of simvastatin-loaded chitosan–PLGA nano hydrogel scaffolds as an advanced therapeutic strategy in regenerative endodontics, offering enhanced biological outcomes compared to conventional approaches.

References

1. Chang PC, Tai WC, Luo HT, Lai CH, Lin HH, Lin ZJ, Chang YC, Lee BS. Core-Shell poly-(D,l-Lactide-co-Glycolide)-chitosan Nanospheres with simvastatin-doxycycline for periodontal and osseous repair. Int J Biol Macromol. 2020 May 7;158:627-635. doi: 10.1016/j.ijbiomac.2020.04.183. Epub ahead of print. PMID: 32387616.
2. Yang F, Cabe M, Nowak HA, Langert KA. Chitosan/poly(lactic-co-glycolic)acid Nanoparticle Formulations with Finely-Tuned Size Distributions for Enhanced Mucoadhesion. Pharmaceutics. 2022 Jan 1;14(1):95. doi: 10.3390/pharmaceutics14010095. PMID: 35056991; PMCID: PMC8778482.
3. Cassiano FB, Soares DG, Bordini EAF, Anovazzi G, Hebling J, Costa CAS. Simvastatin-Enriched Macro-Porous Chitosan-Calcium-Aluminate Scaffold for Mineralized Tissue Regeneration. Braz Dent J. 2020 Sep 4;31(4):385-391. doi: 10.1590/0103-6440202003252. PMID: 32901714.
4. Alsaeed MA, Al-Ghaban NMH. Chitosan Nanoparticle/Simvastatin for Experimental Maxillary Bony Defect Healing: A Histological and Histomorphometrical Study. Biomimetics (Basel). 2023 Aug 14;8(4):363. doi: 10.3390/biomimetics8040363. PMID: 37622968; PMCID: PMC10452510.
5. Soares DG, Bordini EAF, Bronze-Uhle ES, Cassiano FB, Silva ISP, Gallinari MO, Matheus HR, Almeida JM, Cintra LTA, Hebling J, de Souza Costa CA. Chitosan-Calcium-Simvastatin Scaffold as an Inductive Cell-Free Platform. J Dent Res. 2021 Sep;100(10):1118-1126. doi: 10.1177/00220345211024207. Epub 2021 Jul 27. PMID: 34315311.
6. Bronze-Uhle ES, Melo CCDSB, da Silva ISP, Stuani VT, Bueno VH, Rinaldo D, de Souza Costa CA, Lisboa Filho PN, Soares DG. Simvastatin-Loaded Chitosan Microspheres as a Biomaterial for Dentin Tissue Engineering. J Biomed Mater Res B Appl Biomater. 2025 Feb;113(2):e35536. doi: 10.1002/jbm.b.35536. PMID: 39888107.
7. Gallinari MO, Bordini EAF, Furquim EMA, de Toledo PTA, Stuani VT, Barra RHD, Ervolino E, Cintra LTA, de Souza Costa CA, de Almeida JM, Soares DG. Chitosan-calcium-simvastatin scaffold for bone repair under inflammation. Int

J Biol Macromol. 2026 Mar;350:151039. doi: 10.1016/j.ijbiomac.2026.151039. Epub 2026 Feb 20. PMID: 41724295.

8. Murali VP, Guerra FD, Ghadri N, Christian JM, Stein SH, Jennings JA, Smith RA, Bumgardner JD. Simvastatin loaded chitosan guided bone regeneration membranes stimulate bone healing. J Periodontal Res. 2021 Oct;56(5):877-884. doi: 10.1111/jre.12883. Epub 2021 Apr 8. PMID: 33830521.
9. Peters AA, Kaur C, Cabe M, Langert KA, Maier K, Gahtan V. Simvastatin-Loaded Chitosan-Functionalized PLGA Nanoparticles: Characterization and Use in Intimal Hyperplasia Therapy. Pharmaceutics. 2025 Mar 20;17(3):391. doi: 10.3390/pharmaceutics17030391. PMID: 40143054; PMCID: PMC11944580.
10. Alzahrani RF, Almuqati MS, AlAli SA, Alamer KA, Rabbani S, Alqahtani MS, Bakheit AH, Asiri HH, Harisa GI. Folate- and chitosan-functionalized lipid nanoparticles for co-delivery of pioglitazone and simvastatin to enhance hepatic cancer therapy: effects on IL-1β, IL-6, BCL2/BAX gene expression, and GPX4, COX-2, and MMP-9 activities. Mol Biol Rep. 2025 Sep 19;52(1):926. doi: 10.1007/s11033-025-11011-2. PMID: 40971053.
11. Chang PC, Tai WC, Luo HT, Lai CH, Lin HH, Lin ZJ, Chang YC, Lee BS. Core-Shell poly-(D,l-Lactide-co-Glycolide)-chitosan Nanospheres with simvastatin-doxycycline for periodontal and osseous repair. Int J Biol Macromol. 2020 May 7;158:627-635. doi: 10.1016/j.ijbiomac.2020.04.183. Epub ahead of print. PMID: 32387616.
12. Sinha, Preksha & Kumari, Anukriti & Priya, Prerna & Kumar, Sumana & Kashwani, Ritik. (2025). Chitosan-Based Innovations for Microplastic Mitigation in Dentistry: Environmental Impact, Technological Advancements, and Future Perspectives: A Comprehensive Review. IOSR Journal of Dental and Medical Sciences. 24. 61-66. 10.9790/0853-2401046166.
13. Soares DG, Anovazzi G, Bordini EAF, Zuta UO, Silva Leite MLA, Basso FG, Hebling J, de Souza Costa CA. Biological Analysis of Simvastatin-releasing Chitosan Scaffold as a Cell-free System for Pulp-dentin Regeneration. J Endod. 2018 Jun;44(6):971-976.e1. doi: 10.1016/j.joen.2018.02.014. Epub 2018 Apr 24. PMID: 29703618.
14. Atia, G. A. N., Shalaby, H. K., Zehravi, M., Ghobashy, M. M., Attia, H. A. N., Ahmad, Z., Khan, F. S., Dey, A., Mukerjee, N., Alexiou, A., Rahman, M. H., Klepacka, J., & Najda, A. (2022). Drug-Loaded Chitosan Scaffolds for Periodontal Tissue Regeneration. Polymers, 14(15), 3192. https://doi.org/10.3390/polym14153192
15. Liu H, Lu J, Jiang Q, Haapasalo M, Qian J, Tay FR, Shen Y. Biomaterial scaffolds for clinical procedures in endodontic regeneration. Bioact Mater. 2021 Oct 14;12:257-277. doi: 10.1016/j.bioactmat.2021.10.008. PMID: 35310382; PMCID: PMC8897058.