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Short Communication

Nitrofurantoin as an intracanal medicament: A promising alternative or a passing trend?

Lipika Jain[1]*, Ravi Gupta[2], Mrinalini Jaichander[1], Deepthi M[1]

[1]Dept. of Conservative Dentistry and Endodontics, Dayananda Sagar College of Dental Sciences, Bengaluru, Karnataka, India

[2]Dept. of Conservative Dentistry and Endodontics, Manipal University College Malaysia (MUCM), Jalan Batu Hampar, Bukit Baru, Melaka, Malaysia

Abstract

The pursuit of an ideal intracanal medicament remains a central focus in endodontic research and clinical practice. Nitrofurantoin, a synthetic nitrofuran antibiotic primarily used in the treatment of urinary tract infections, has recently gained attention for its potential application in endodontics. This article explores the rationale for using nitrofurantoin as an intracanal medicament and evaluates the current evidence supporting its antimicrobial efficacy. Preliminary in vitro studies demonstrate promising results, particularly against resistant endodontic pathogens such as Enterococcus faecalis. However, despite these encouraging findings, in vivo and clinical data remain scarce. Additionally, concerns related to antibiotic resistance, potential allergenicity, and regulatory considerations must be addressed before its widespread clinical adoption. As endodontic practice increasingly embraces evidence-based and patient-centered approaches, the integration of nitrofurantoin into intracanal protocols must be supported by comprehensive clinical trials and standardized guidelines. This article highlights the need for further investigation to determine whether nitrofurantoin represents a meaningful advancement in endodontic therapy or merely a passing trend.

Keywords: Intracanal medicament, Endodontics, Antimicrobial, Enterococcus faecalis, Biofilm, Triple antibiotic paste, Calcium hydroxide.

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1. Introduction

Endodontic infections are polymicrobial in nature, with bacterial biofilms forming within the root canal system. Various microbial species can be identified in primary periapical infections; however, in secondary infections, *Enterococcus faecalis* (*E. faecalis*) is the most prevalent bacterium.[1] *E. faecalis* is a facultative anaerobic, gram-positive bacterium and an opportunistic pathogen that resides naturally in the oral cavity. It is the most commonly isolated species in persistent and secondary endodontic infections.[2] Studies have shown that *E. faecalis* is present in 24–70% of root canal failures based on culture methods and 67–77% using molecular techniques, with some reports identifying it in up to 90% of cases.[3] Its survival in treated root canals is attributed to its ability to withstand harsh environmental conditions, penetrate deeply into dentinal tubules, and develop antimicrobial resistance.[4]

The main aim of endodontic treatment is to eradicate microbial infections, prevent reinfection, and promote periapical healing. Chemomechanical preparation of the root canal is the first step in eliminating intracanal bacterial invasion. However, chemomechanical procedures alone cannot ensure complete disinfection of the root canal system, allowing microorganisms to persist within the complex anatomy. Therefore, rigorous irrigation protocols and the use of intracanal medicaments are essential to reinforce disinfection and prolong antimicrobial contact time.[5]

*Corresponding author: Lipika Jain
Email: drlipikajain@gmail.com

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1.1. Challenges with current intracanal medicament

Among the commonly used intracanal medicaments, calcium hydroxide (Ca (OH) $_2$) has been extensively studied for its antimicrobial properties and ability to neutralize bacterial endotoxins. However, *E. faecalis* exhibits resistance to $Ca(OH)_2$ by thriving in alkaline environments up to pH 11.1 due to the presence of a proton pump that resists the alkaline effects. The pH required to kill *E. faecalis* is 11.5, which cannot be achieved with $Ca(OH)_2$, as its pH is only 10.3.[6] Additionally, dentin reduces the pH gradient from the inner to the peripheral root portion, further limiting the efficacy of $Ca(OH)_2$. Moreover, systematic reviews have reported that while $Ca(OH)_2$ reduces endotoxin levels, it does not eliminate lipopolysaccharides (LPS), necessitating the exploration of alternative agents.[7]

Local applications of antibiotics as intracanal medicaments have been used in endodontics since the 1950s with Grossman's polyantibiotic paste.[8] Local application is often more effective than systemic administration as it ensures direct drug delivery to the infected site, bypassing the risks associated with systemic antibiotics such as side effects, resistance development, and patient compliance. However, improper use of local antibiotics can also lead to bacterial resistance and facilitate the transfer of resistance genes.[9,10]

Triple antibiotic paste (TAP), a combination of metronidazole, ciprofloxacin, and minocycline, has been widely used due to its potent antimicrobial properties. However, its effectiveness against *E. faecalis* remains inconsistent, possibly due to bacterial resistance. Furthermore, the presence of minocycline in TAP can lead to crown discoloration, posing an aesthetic concern.[11,12] To overcome these limitations, modified triple antibiotic paste (MTAP), which substitutes minocycline with clindamycin, and double antibiotic paste (DAP), containing only ciprofloxacin and metronidazole, were introduced. Despite these modifications, antibiotic resistance remains a significant challenge, emphasizing the need for alternative medicaments that offer both efficacy and sustainability in endodontic treatment.

1.2. Nitrofurantoin as an alternative intracanal medicament

Nitrofurantoin, a broad-spectrum antibacterial agent commonly prescribed for multidrug-resistant urinary tract infections (UTIs), has gained attention in endodontics due to its potential efficacy against resistant bacterial strains, particularly *E. faecalis*. It is a synthetic antimicrobial derived from furan with a nitro group and a hydantoin side chain. Nitrofurantoin is effective against most gram-positive and gram-negative organisms, including *Escherichia coli*, *Enterococci*, *Klebsiella*, and *Staphylococcus saprophyticus*. The U.S. Food and Drug Administration (FDA) approved nitrofurantoin in 1953 to treat lower urinary tract infections.[13]

2. Mechanism of Action

Nitrofurantoin exerts its bactericidal and bacteriostatic effects through a unique multi-target mechanism, making it less susceptible to bacterial resistance. Unlike many antibiotics that act on a single cellular process, nitrofurantoin disrupts multiple essential bacterial functions.[14]

1. Intracellular activation
    a. Nitrofurantoin is taken up by bacterial cells, where it is enzymatically reduced by flavoproteins (such as nitrofuran reductase).
    b. This reduction generates highly reactive intermediates that interfere with bacterial metabolism.
2. Disruption of Vital Cellular Processes
    a. The reactive metabolites of nitrofurantoin bind to and inhibit several key bacterial enzymes, leading to:
    b. Inhibition of DNA and RNA synthesis, preventing bacterial replication.
    c. Disruption of protein synthesis, impairing bacterial growth and function.
    d. Inhibition of aerobic energy metabolism, depleting ATP production.
    e. Interference with cell wall synthesis, compromising bacterial structural integrity.
3. Reduced Resistance Development
    a. Nitrofurantoin's multi-faceted mechanism makes it difficult for bacteria to develop resistance.
    b. However, mutations in *nfsA* and *nfsB* genes, which encode nitrofuran reductases in *E. coli*, can confer resistance by reducing drug activation.

3. Formulation and Concentration

Nitrofurantoin at concentrations of 12.5 mg/mL and 25 mg/mL is biocompatible with rat subcutaneous connective tissue, demonstrating its safety for clinical applications.[15] Most studies have used nitrofurantoin at 25 mg/mL (minimum inhibitory concentration) in gel form.

4. Clinical Applications and Efficacy

4.1. Persistent endodontic infections

Alrahman et al. evaluated nitrofurantoin as an intracanal medicament and found that at 25 mg/mL, nitrofurantoin effectively eliminated *E. faecalis* after 7 days. When compared with TAP, nitrofurantoin demonstrated complete eradication of *E. faecalis* at 12.5 mg/mL and above, whereas TAP required 25 mg/mL to achieve similar results. Nitrofurantoin's efficacy at lower concentrations, particularly against resistant strains, highlights its potential as a superior alternative to TAP.[5]

4.2. Symptomatic irreversible pulpitis

In a study by Abbasi et al., nitrofurantoin paste at 100 mg/mL concentrations was applied in the root canal of patients with

symptomatic irreversible pulpitis. A majority of the patients reported decreased pain scores at different time intervals, with over half experiencing complete pain relief within 72 hours. These findings suggest that nitrofurantoin, along with DAP, can be effectively used as an intracanal medicament to manage symptomatic irreversible pulpitis.[16]

4.3. Regenerative endodontics

The American Association of Endodontics (AAE) recommends calcium hydroxide or 1–5 mg/mL concentrations of TAP or DAP for disinfecting root canals in regenerative endodontics.[17] However, concerns regarding the disinfection efficacy of these combinations at lower concentrations have been raised. Recent studies suggest that nitrofurantoin, known for its potent antimicrobial activity against *E. faecalis* and *Candida albicans*, demonstrates efficacy comparable to conventional medicaments. The use of nitrofurantoin gel at a concentration of 1 mg/mL has shown potential in overcoming unwanted drug interactions associated with multidrug combinations.[10]

4.4. Teeth with necrotic pulp and primary infections

Elasaber et al. demonstrated that nitrofurantoin rendered 79% of root canals free from cultivable aerobic bacteria and 93% free from cultivable anaerobic bacteria, compared to 35.7% and 79%, respectively, for $Ca(OH)_2$. Although no statistically significant difference was noted, the superior antimicrobial properties of nitrofurantoin highlight its promise as a root canal medicament in clinical situations.[6]

4.5. Intratubular radicular dentin penetration of nitrofurantoin

Effective intracanal medicaments must penetrate deeply into dentinal tubules to eliminate intracanal bacteria and prevent recurrent infections. Nitrofurantoin has demonstrated superior penetration into dentinal tubules, particularly in the apical third, compared to TAP and $Ca(OH)_2$. Its minuscule particle size facilitates deeper infiltration into dentin, enabling it to eliminate pathogens residing in the tubules.[18]

5. Adverse Effects and Safety

The safety profile of nitrofurantoin in endodontic applications requires further research. Although it is well tolerated in systemic use, potential cytotoxicity and tissue irritation in periapical tissues need to be studied. Compared to traditional antibiotics, nitrofurantoin's unique mechanism of action minimizes the risk of resistance development, making it a safer alternative in the long term.

6. Future Directions

Recent in vitro studies have demonstrated that replacing minocycline with nitrofurantoin in the Hoshino paste formulation, at a minimum inhibitory concentration (MIC) of 4 mg, combined with ciprofloxacin (1 mg) and metronidazole (5 mg), effectively reduced microbial counts in the root canal system.[12] Despite these promising results, the routine use of nitrofurantoin in endodontics must be approached with caution to prevent unnecessary antibiotic exposure and mitigate the risk of resistance development. Despite its potential, the routine use of nitrofurantoin in endodontics must be carefully regulated to prevent unnecessary antibiotic exposure and resistance development.

Future research should focus on:

1. Long-term effects on periapical healing
2. Optimization of formulation for intracanal application
3. Comparative studies with other intracanal medicaments and irrigation techniques
4. Efficacy against other microorganisms found in polymicrobial infections

7. Conclusion

Nitrofurantoin has demonstrated strong antibacterial efficacy against *E. faecalis*, with minimal resistance development, making it a promising alternative to conventional intracanal medicaments. Its broad-spectrum action, effectiveness at low concentrations, and minimal systemic absorption make it an attractive option for endodontic applications. However, further studies are required to evaluate its long-term effects and safety profile before widespread clinical adoption.

8. Source of Funding

None.

9. Conflict of Interest

None.

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