N-acetylcysteine as an antimicrobial therapeutic alternative against bacterial pathogens associated with peri-implantitis

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Dental implants represent one of the main modalities for oral rehabilitation, exhibiting high clinical success rates. However, biological complications, particularly peri-implant infections, remain a significant therapeutic challenge. Peri-implantitis is associated with the formation of complex polymicrobial biofilms that are highly resistant to conventional antimicrobials, involving classical periodontopathogens such as *Porphyromonas gingivalis* and *Prevotella intermedia*, as well as opportunistic species like *Staphylococcus aureus*. Although chlorhexidine (CHX) is considered the gold standard among antimicrobial agents, its cytotoxicity and reduced efficacy against mature biofilms reinforce the need for new therapeutic approaches. In this context, N-acetylcysteine (NAC) has emerged as a promising agent due to its antimicrobial potential and its ability to interfere with the extracellular matrix of biofilms. This study evaluated, *in vitro*, the antimicrobial activity of NAC against *S. aureus*, *P. gingivalis*, and *P. intermedia* by determining the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), in comparison with 0.12% CHX. Additionally, the effect of NAC on mature *S. aureus* biofilms formed on titanium discs, material widely used in dental implant fabrication, was investigated at different exposure times. MIC assays were performed using broth microdilution in 96-well plates, with microbial growth assessed through turbidity analysis and a metabolic resazurin assay, followed by subculture to determine MBC. For biofilm assays, specimens were subjected to treatments for 1 and 5 minutes, followed by microbiological quantification by counting colony-forming units (CFU/mL). Biofilm morphology and structural integrity were evaluated using Scanning Electron Microscopy (SEM). The results demonstrated consistent antimicrobial activity of NAC against all tested species, with MIC values of 3.125 mg/mL for *S. aureus* and 6.25 mg/mL for *P. gingivalis* and *P. intermedia*. NAC exhibited bactericidal effects at 6.25 mg/mL for *S. aureus* and *P. gingivalis*, whereas *P. intermedia* showed greater tolerance, with an MBC of 12.5 mg/mL. In mature biofilm models, the positive control group showed high microbial counts, ranging from 10^9 to 10^{11} CFU/mL. CHX drastically reduced bacterial viability, with counts between 10^3 and 10^5 CFU/mL. NAC significantly reduced microbial load, although in a time-dependent manner. After 1 minute of treatment, variable reductions were observed among samples, with values ranging from 0 to 1.63×10^5 CFU/mL. After 5 minutes, a more homogeneous and pronounced reduction was observed, with counts below 10^3 CFU/mL in all evaluated samples, representing an approximate 6–8 log reduction compared to the positive control and even surpassing the effect observed with CHX. SEM analyses corroborated the antimicrobial findings, revealing structural disorganization of the biofilm, reduced bacterial density, and more pronounced morphological alterations after 5 minutes of NAC exposure. In conclusion, NAC exhibits antimicrobial activity against pathogens associated with peri-implantitis, including a significant effect on

mature *S. aureus* biofilms. Increased exposure time enhanced antimicrobial efficacy and promoted greater biofilm disruption, highlighting NAC as a promising candidate for the development of new therapeutic approaches in implant dentistry.

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