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Impact of Nanoparticle-Encapsulated Artemisinin Versus Standard Artemisinin on Parasite Clearance in Severe Malaria: A Review

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ABSTRACT

Severe malaria, predominantly caused by *Plasmodium falciparum*, is a major contributor to global malaria mortality. Standard artemisinin formulations, such as artesunate and artemether, provide rapid parasite clearance but are limited by poor water solubility, short half-life, and emerging resistance threats, necessitating improved therapeutic strategies. This review compared nanoparticle-encapsulated artemisinin with standard artemisinin formulations in terms of parasite clearance efficacy in severe malaria. A narrative synthesis was conducted evaluating published studies on pharmacokinetics, pharmacodynamics, in vitro and in vivo efficacy, safety, and translational prospects of nanoparticle-encapsulated versus standard artemisinin in severe malaria treatment. Standard artemisinin rapidly reduces parasite biomass and remains the therapeutic gold standard. However, nanoparticle-encapsulated artemisinin formulations, including lipid-based, polymeric, and metallic nanoparticles, demonstrate enhanced solubility, prolonged systemic circulation, and targeted delivery, resulting in superior parasite clearance in preclinical models. Lipid and polymeric nanoparticles provide controlled release and improved bioavailability, while metallic nanoparticles show dual antiplasmodial effects, though their toxicity profiles necessitate caution. Despite promising laboratory and animal study outcomes, nanoparticle formulations have not advanced to human trials due to challenges in manufacturing scalability, regulatory approval, and cost-effectiveness for malaria-endemic settings. Nanoparticle-encapsulated artemisinin shows potential to enhance parasite clearance compared to standard formulations, but rigorous clinical trials and safety evaluations are required before integration into severe malaria treatment protocols. Future research should prioritise translational studies to establish efficacy, safety, and affordability to advance malaria management globally.

Keywords: Nanoparticle-encapsulated artemisinin**,** Severe malaria treatment**,** Parasite clearance**,** Antimalarial nanomedicine**,** Standard artemisinin therapy.

INTRODUCTION

Malaria continues to pose a significant global health burden, with severe malaria contributing substantially to morbidity and mortality, particularly among young children in sub-Saharan Africa and Southeast Asia [1, 2]. Severe malaria, commonly caused by *Plasmodium falciparum*, is characterised by high parasitaemia and life-threatening complications such as cerebral malaria, metabolic acidosis, severe anaemia, and multi-organ failure [3, 4]. Prompt and effective parasite clearance is critical in reducing mortality and improving clinical outcomes in severe malaria.

Artemisinin and its derivatives have been the cornerstone of malaria chemotherapy due to their rapid schizonticidal activity [5]. Standard artemisinin formulations, administered intravenously as artesunate or intramuscularly as artemether, demonstrate swift parasite clearance, significantly reducing parasite biomass within the first 24 hours of treatment initiation [6]. However, limitations such as poor water solubility, short half-life, and potential for resistance emergence pose challenges to their sustained efficacy.

Recent advances in nanotechnology have led to the development of nanoparticle-encapsulated artemisinin formulations aimed at overcoming these pharmacokinetic and pharmacodynamic limitations [7, 8]. Encapsulation

within lipid-based, polymeric, or metallic nanoparticles enhances drug solubility, bioavailability, and controlled release, potentially improving therapeutic outcomes in severe malaria management. Moreover, targeted delivery using functionalised nanoparticles may reduce off-target toxicity and required dosing frequency. This review compares the impact of nanoparticle-encapsulated artemisinin with standard artemisinin formulations on parasite clearance in severe malaria. It synthesises evidence on their pharmacological profiles, mechanisms of enhanced activity, in vitro and in vivo efficacy, safety profiles, and translational prospects in clinical practice. By systematically examining these aspects, the review aims to inform future research directions and therapeutic strategies for optimising severe malaria treatment outcomes in endemic regions.

Pharmacological Profiles of Artemisinin Formulations

i. **Standard Artemisinin:** Standard artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin) exert antimalarial activity by generating reactive oxygen species and carbon-centred radicals upon activation by intraparasitic haem or ferrous ions, causing damage to parasite proteins and membranes [9]. Despite rapid parasite clearance, their pharmacokinetic limitations include low aqueous solubility and rapid systemic clearance, necessitating frequent dosing and combination with partner drugs to prevent recrudescence and resistance emergence.

ii. **Nanoparticle-Encapsulated Artemisinin:** Nanoparticle encapsulation strategies seek to overcome these limitations by enhancing drug solubility, stability, and bioavailability. Lipid-based nanoparticles such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) improve solubility and prolong systemic circulation [10]. Polymeric nanoparticles (e.g. PLGA, chitosan) enable controlled and sustained release, while metallic nanoparticles (e.g. gold, silver) may synergise antimalarial effects via intrinsic parasite toxicity. Functionalisation with targeting ligands (e.g. antibodies, peptides) can enable selective delivery to infected erythrocytes or parasite-infected tissues.

Mechanisms of Enhanced Parasite Clearance

Nanoparticle-encapsulated artemisinin formulations enhance parasite clearance through:

i. **Improved Solubility and Bioavailability:** Encapsulation increases aqueous solubility and oral absorption, enabling higher systemic concentrations at therapeutic sites [11].

ii. **Prolonged Circulation Time:** Reduced clearance and controlled release maintain effective plasma concentrations for longer durations, enhancing schizonticidal activity.

iii. **Targeted Delivery:** Functionalised nanoparticles increase accumulation in infected erythrocytes or cerebral microvasculature, improving efficacy in severe manifestations such as cerebral malaria [12, 13].

iv. **Synergistic Effects:** Metallic nanoparticles may generate reactive oxygen species or disrupt parasite membranes, complementing artemisinin's mechanism.

Evidence from In Vitro Studies

Several in vitro studies have evaluated nanoparticle-encapsulated artemisinin formulations against *P. falciparum* strains. Lipid-based nanoparticles loaded with artemisinin have demonstrated significantly lower IC50 values compared to free drug, indicating enhanced potency [14, 15]. Polymeric nanoparticles show controlled release profiles with sustained antiparasitic activity over extended durations, potentially reducing dosing frequency.

Metallic nanoparticles conjugated with artemisinin exhibit potent antiplasmodial activity through dual mechanisms of nanoparticle-mediated toxicity and artemisinin-induced free radical generation. However, cytotoxicity profiles against human cells vary depending on nanoparticle type, size, and surface charge, necessitating careful formulation optimisation.

Evidence from In Vivo Animal Studies

In vivo murine models of *P. berghei* infection have demonstrated superior parasite clearance rates and survival outcomes with nanoparticle-encapsulated artemisinin compared to standard formulations [16]. For instance, artemisinin-loaded SLNs and PLGA nanoparticles have shown prolonged half-life, higher peak plasma concentrations, and reduced parasitaemia levels.

Functionalised nanoparticles targeting infected erythrocytes or endothelial adhesion molecules have shown enhanced cerebral parasite clearance in experimental cerebral malaria models, reducing neurological sequelae and improving survival. However, translational challenges remain in scaling nanoparticle synthesis, ensuring reproducibility, and confirming safety profiles in higher-order animals.

Safety and Toxicity Considerations

Standard artemisinin formulations are generally well tolerated, with adverse effects primarily related to injection site reactions, transient neutropenia, or neurotoxicity at high doses. Nanoparticle formulations, while enhancing efficacy, may introduce new toxicity concerns depending on nanoparticle composition. Lipid-based and

biodegradable polymeric nanoparticles demonstrate favourable biocompatibility, whereas metallic nanoparticles risk organ accumulation, oxidative stress induction, and long-term toxicity [17].
Comprehensive toxicological evaluations, including genotoxicity, immunotoxicity, and reproductive toxicity studies, are essential before clinical translation of nanoparticle-encapsulated artemisinin formulations to ensure safety in vulnerable populations such as pregnant women and young children.

Clinical Translation Prospects

Despite promising preclinical outcomes, nanoparticle-encapsulated artemisinin formulations are yet to progress to human clinical trials for severe malaria treatment. Nevertheless, their potential to enhance therapeutic efficacy, reduce dosing frequency, and mitigate resistance emergence renders nanoparticle-encapsulated artemisinin a promising future strategy in severe malaria management. Key challenges include:

i. **Manufacturing Scale-Up:** Achieving consistent large-scale production under GMP conditions with stringent quality control [18].
ii. **Regulatory Approvals:** Navigating complex regulatory frameworks for nanoparticle-based therapeutics, requiring extensive safety and efficacy data.
iii. **Cost-Effectiveness:** Ensuring affordability for malaria-endemic low-resource settings to achieve equitable access.

Comparative Summary of Efficacy

A comparative evaluation indicates that while standard artemisinin formulations provide rapid parasite clearance, nanoparticle encapsulation significantly enhances pharmacokinetic profiles, prolongs therapeutic concentrations, and improves targeted delivery. This results in faster and more sustained parasite clearance in preclinical models, with potential clinical implications for reducing mortality and preventing complications in severe malaria.

Integration into Malaria Treatment Protocols

Integration of nanoparticle-encapsulated artemisinin into existing malaria treatment protocols would require:

i. **Establishing Clinical Efficacy:** Conducting phase I-III trials to confirm safety, dosing regimens, and therapeutic superiority of over standard formulations [19].
ii. **Combination Therapy Strategies:** Evaluating encapsulated artemisinin in combination with partner drugs within nanoparticle systems to enhance antimalarial potency and resistance prevention.
iii. **Policy Adaptation:** Updating WHO treatment guidelines upon evidence-based validation to incorporate nanoparticle therapeutics into severe malaria management algorithms.

Research Gaps and Future Directions

Future research should prioritise translational studies bridging preclinical efficacy to clinical application, fostering interdisciplinary collaborations between nanotechnology scientists, pharmacologists, clinical researchers, and malaria control programmes to achieve tangible therapeutic advances. Key research gaps include:

i. Optimising nanoparticle formulations for maximal bioavailability and minimal toxicity [20].
ii. Evaluating pharmacokinetics, pharmacodynamics, and immunogenicity in non-human primate models.
iii. Assessing potential for large-scale GMP manufacturing and cost implications.
iv. Conducting stakeholder consultations in endemic countries to address acceptability and health system integration challenges.

CONCLUSION

In conclusion, nanoparticle-encapsulated artemisinin formulations offer a promising advancement over standard artemisinin in severe malaria treatment by enhancing drug solubility, bioavailability, and targeted delivery, resulting in superior parasite clearance demonstrated in preclinical studies. While standard artemisinin formulations remain the current therapeutic gold standard with proven clinical effectiveness and established safety profiles, their pharmacokinetic limitations necessitate novel strategies to optimise treatment outcomes and prevent resistance emergence. Nanoparticle encapsulation addresses these limitations, potentially transforming severe malaria management by enabling controlled release, sustained plasma concentrations, and site-specific targeting, thereby enhancing therapeutic efficacy and reducing mortality. However, significant challenges remain in translating these formulations to clinical practice, including ensuring biocompatibility, manufacturing scalability, regulatory approval, and cost-effectiveness for resource-limited settings. Rigorous multidisciplinary research encompassing formulation optimisation, comprehensive toxicological evaluations, and phased clinical trials is essential to realise the full potential of nanoparticle-encapsulated artemisinin as a next-generation antimalarial therapy. Integrating such innovative nanomedicine approaches within existing malaria treatment frameworks could significantly advance global efforts towards reducing severe malaria mortality and achieving malaria elimination targets.

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