Nano-Magnetically Targeted Drug Delivery System for Treating Atrial Fibrillation

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ABSTRACT

NanoMed Targeting Systems (NTS) is developing magnetically targeted drug delivery system for treating atrial fibrillation. The system is based on proprietary nanomagnetic-particles attached to the payload, and its noninvasive proprietary magnetic guiding system. Atrial fibrillation (AF) is the most common heart rhythm disorder and a leading cause of strokes. An estimated 2.7–6.1 million people in the United States have AF. With the aging of the U.S. population, this number is expected to increase[1]. Currently, nearly half the patients will become drug refractory and most will require interventions such as catheter ablations—the current standard of care. Ablations carry risks of serious complications and are very costly (5year success <50%). The rapidly rising demand for ablations is already straining the ability to meet treatment demand, and a noninvasive approach that produces satisfactory success rates is lacking. A safer, faster, more effective, and less costly procedure is needed. NTS's innovative procedure is targeting the GPs neural centers on the heart with magnetically targeted nanoparticles containing a substance to shut off their activities. The nanoparticle solution is introduced into the coronary circulation, whereupon the particles are immediately captured by a magnetic field over and guided to the treatment area.

We are developing a Magnetic Workstation, a continuously variable electromagnet that is external to the patient, with three-dimensional positioning with respect to the heart, to capture the particles and target them. Our procedure will be less invasive, less expensive, and less risky. The technology for cardiac arrhythmia applications has been demonstrated in preclinical dogs' trials.

Keywords: atrial fibrillation, magnetic nanoparticles, targeted drug delivery, autonomic nervous system.

INTRODUCTION

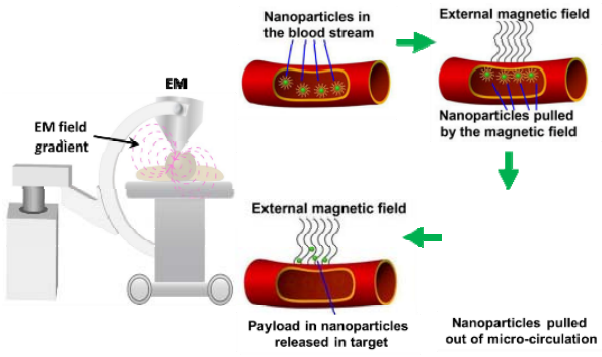
Preclinical and clinical studies indicated that a hyperactive state of the cardiac autonomic nervous system (CANS) is critical in initiating and perpetuating atrial fibrillation (AF)[2,3,4]. The atrial CANS converge at several ganglionated plexi (GP) that serve as the integration centers of the CANS. These circumferential lines also transect 3 of the 4-major atrial GP, indicating that GP ablation may Recent clinical trial indicated that suppression of the GP function was effective in treating paroxysmal AF[5].

Targeted drug delivery using super-paramagnetic nanoparticles (MNP) is a technology in which medicines are targeted to selected tissues by using external magnetic field, to maximize therapeutic efficacy and minimize side effects and costs[6,7]. NanoMed Targeting Systems (NTS) is developing magnetically targeted drug delivery systems for treating atrial fibrillation. The system is based on proprietary nanomagnetic-particles attached to the payload, and its noninvasive proprietary magnetic guiding system. Previously, studies done by NTS demonstrated that after intracoronary injection, MNP carrying a neurotoxic agent could be magnetically targeted to the GP and suppressed GP function[8].

In 2015-2016 we have conducted dogs' studies using $CaCl_2$ as the neuron suppressor agent. We demonstrated the targeted GP neural activity was suppressed 15 minutes from inserting of nano formulation into the blood stream and activating the magnetic field. Three weeks following the procedure, the GPs remain in-active, and AF could not be induced.

NTS TECHNOLOGY PLATFORM

PLGA (poly-lactic-co-glycolic acid) loaded with and $CaCl_2$ magnetite nanoparticles were formulated and was intracoronary injected. A custom electromagnet (EM), capable of producing 2600 gauss of field strength at the epicardial surface of targeted GP, was designed and constructed. The schematic description of the system is shown in the following illustration:



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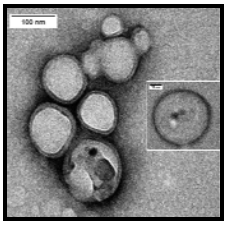
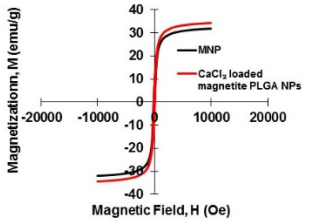
The following chart shows the physical properties of the nano-formulation:

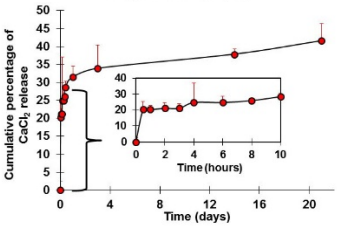
Transmission electron micrograph of $CaCl_2$ loaded magnetite PLGA nanoparticles (Ca-MNP) shows spherical particles of average size ~120 nm. Scale bar is 100 nm wide. Inset image shows MNP loaded in single PLGA nanoparticle. Scale bar is 50 nm wide.



Magnetic hysteresis loops of bare MNPs and Ca-MNPs exhibiting superparamagnetic behaviors



Cumulative percent release of $CaCl_2$ from Ca-MNP at 37°C over 21 days. Inset, release kinetics of $CaCl_2$ from particles in the first 10 hours.



Pre-Clinical Trials

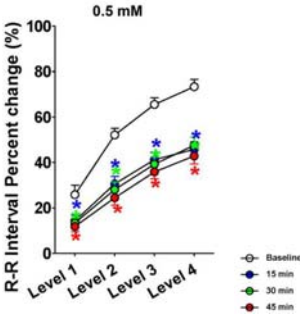
GP function was measured by the maximal heart rate slowing response, specifically R-R interval prolongation induced by high frequency stimulation (HFS) of the. Each attempt of HFS lasted less than 30 seconds and the next measurement was not taken until the R-R intervals returned to the baseline levels.

3 major GPs received microinjections of saline or $CaCl_2$ in the trials - the anterior right GP (ARGP), inferior right GP (IRGP) and superior left GP (SLGP). The inferior left GP (ILGP) was not injected due to its location.

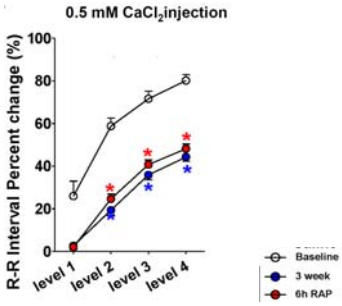
Ca-MNP was slowly infused into the circumflex artery. The nano-formulation was pulled out of the microcirculation into the GP by external magnetic field generated by 2600 gauss electromagnet. The magnetic field was designed to generate focal point on a small area that covers the GP.

RESULTS

0.5 mM of $CaCl_2$ was microinjected into 6 animals, 18 GP in total. A decreased R-R interval prolongation response was found at all levels of stimulation voltage. The maximal effect occurred within 15 minutes of $CaCl_2$ injection.



Twelve other animals were equally divided into two groups: (1) saline injection; (2) 0.5 mM $CaCl_2$. Decreased R-R interval prolongation was observed in the $CaCl_2$ group both 3 weeks after $CaCl_2$ micro-injection and after 6 hours of RAP.



CONCLUSION

NTS new nano-technology procedure using $CaCl_2$ is capable of inhibiting GP function acutely and preventing RAP-induced atrial remodeling 3 weeks later. This is a new procedure to treat paroxysmal AF, whose invasiveness is similar to a routine coronary arteriography. The three components of Ca-MNP are either endogenous substances of the human body or will be metabolized to endogenous substances, thereby minimizing toxicity and systemic side effects.

AF is a progressive disease and ideally should be intervened in its very early stage. Anti-arrhythmic agents, with their side effects and relatively low efficacy, usually only work for a limited period of time. RF ablation, with its relatively low success rate, serious complications, and potential of introducing iatrogenic atrial tachycardias, is reserved only for highly symptomatic, drug-refractory patients to be performed by well-trained electrophysiologists. With the anticipated increase of AF patients in the near future, NTS new nano-technology procedure can be performed by all intervention cardiologists on substantially more patients in early stage of AF. Early intervention of AF potentially can prevent AF from progressing to more advanced stages that require expensive anticoagulation and ablative therapies.

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