Perspective

Use of biologically synthesized antimicrobial nanoparticles for improving peritoneal dialysis technique: a translational research perspective

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Peritoneal dialysis (PD) is a well-established renal replacement therapy (RRT) for end-stage renal failure (ESRF) and offers certain clear advantages over hemodialysis. However, PD is often associated with a high risk of infection of the intraperitoneal cavity, subcutaneous tunnel and catheter exit site, which may subsequently form microbial biofilms. Generally, a majority of PD patients suffer from bacterial and fungal infections and if the infection(s) is diagnosed timely, they can be resolved by appropriate antibiotic treatment. However, the immune system of ESRF patients continuing on PD may have been compromised and infections are as frequent as once every 10-15 weeks necessitating frequent use of conventional antimicrobial drugs, which may cause emergence of drug resistance. Further, higher doses of antibiotics are often required for such infections, this may cause intolerable toxicity. Moreover, infections, if correct it as "not resolve and sustain" for a week or more, may lead to infectious peritonitis, which severely affects the functioning of the peritoneal membrane, and its resolution may require hospitalization of the patient.

Clinically, treatment of infectious peritonitis involves rapid resolution of infection by eradicating the causative organism(s) and the preservation of peritoneal membrane function. However, in the majority of severe cases, treatment may fail to resolve the condition even after intravenous and intraperitoneal antibiotics and the patients are switched to hemodialysis, either temporarily or permanently. Switching to hemodialysis is undesirable because of complications associated with temporary vascular access, reduced patient autonomy and increased medical costs. Infectious peritonitis is not only the major cause of technique failure, but also the leading cause of mortality and morbidity in PD patients. Therefore, there is an urgent need to improve the existing PD technique in terms of its efficacy against infections and in vivo adequacy during long-term PD; so that, the frequency of PD associated infections could be reduced during prolonged PD and thereof to reduce the traumatic and life-threatening episodes of infectious peritonitis. Practically, this can be achieved through developing infection resistant PD fluid composition which could provide long term protection against a variety of PD associated infections by bacteria, mycobacteria, fungi or viruses. The key requisite to develop such an efficient and novel composition is that the composition should contain some antimicrobial agents with novel mode of action and multiple molecular targets to tackle microbial resistance. Furthermore, these antimicrobial agents should preserve their efficacy and adequacy (i.e. biocompatibility and non-cytotoxicity) during their frequent and long-term use.

Antimicrobial nanoparticles, especially metal (e.g. gold, silver, titanium and bismuth) and metal oxide (e.g. zinc oxide, titanium oxide, etc.) nanoparticles would be of immense interest owing to their exclusive antimicrobial activity against a variety of infections and potential wound healing and anti-inflammatory properties. Metallic nanoparticles have been researched extensively in the past and some of their classes have been found to...
be very effective in terms of their antimicrobial and anti-
biomfilm properties\[2\]. Mechanistically, these nanoparti-
cles produce their antimicrobial activity through affect-
ing multiple pathways\[2\]. Thus, many concurrent
mutations would have to occur to develop resistance to
these nanoparticles\[5\]. Therefore, antimicrobial for-
mulations based on these nanoparticles could be
administered frequently as required to manage recurrent
and persistent infections during long-term PD with
reduced risk of developing resistance. Studies have
highlighted that naturally occurring bacteria do not
develop antimicrobial resistance against metallic nano-
particles\[4\]; even some of their classes have the potential
to eradicate multidrug-resistant infections when these
are used in combination with antibiotics\[4\, 5\]. Likewise,
some classes can limit biofilm formation either
independently or in combination with antibiotics\[3\].
Owing to such broad spectral antimicrobial properties
and activity against biofilms and formidable multidrug
resistant pathogens, metallic nanoparticles are finding
their potential applications as antimicrobial agents and
disinfectants to improve several biomedical devices,
pharmaceutical products and healthcare interventions
including medicines\[4\, 5\]. Based on these attributes, the
use of metallic nanoparticles can also be envisaged for
developing infection resistant composition of PD fluid
(as depicted in Fig. 1A). The particular advantage of
employing metal based antimicrobial nanoparticles in
this translational research endeavor is that these can be
filter-sterilized and added directly to the PD fluid for
long term storage and prolonged shelf life\[2\]. Further-
more, these can easily withstand temperature variations
(ranging from 4°C to 50°C, which is generally
encountered during transportation and storage of
medical products), under which conventional antibiotics
may inactivate or degrade. Moreover, the preparation of
nanoparticles is cost-effective and relatively simple
compared to antibiotics synthesis\[4\, 7\].

Metallic nanoparticles of varying sizes, shapes, and
properties can be synthesized using variety of chemical
and physical methods. However, these methods often
lead to the presence of some toxic chemicals adsorbed
on the surface and, if are used in pharmaceutical
products or biomedical applications, these could
produce intolerable toxicity and adverse effects to
humans\[2\]. This is not an issue when it comes to
biologically synthesized nanoparticles, i.e. those
synthesized from biomaterials derived from micro-
organisms or plant parts following green chemistry
approach\[6\]. Green synthesis of nanoparticles (using
either plant products or microorganisms) is considered
as environmentally benign and cost-effective replace-
ment to the toxic chemical and physical methods.

Compared to plant mediated synthesis, the synthesis
of nanoparticles using microorganisms is relatively
more tedious and time consuming process, as it requires
more steps in maintaining cell culture, longer incubation
time for intracellular reduction of metal ions and more
steps to purify synthesized nanoparticles. On the other
hand, plant mediated green synthesis of nanoparticles is
relatively simple and provides several clear advan-
tages\[2\] like (a) extracellular and rapid biosynthesis as
water soluble phytochemicals reduce the metal ions in a
much shorter time, (b) no need to maintain time-
consuming microbial cultures and purification steps as
required in microbial mediated biogenic synthesis, (c)
preparation is safe to handle and is free from problems
arising due to microbial contamination, (d) cost
effectiveness as the use of plant extracts reduces the
cost incurring in maintaining microbial cultures and to
isolate and purify the synthesized nanoparticles in
multiple steps, and (e) availability of broad variability of
metabolites that may aid in reduction. The generalized
flowchart for plant mediated nano-biosynthesis is
shown in Fig. 1B.

Studies have shown that biologically synthesized
nanoparticles exhibit better biocompatibility and less
cytotoxicity compared to their counterparts prepared
using chemical or physical methods\[2\]. Here, I envisage
that metal nanoparticles synthesized biologically can
also be used to impart infection resistant properties to
peritoneal dialysis fluid owing to their relatively low in
vivo toxicity and higher biocompatibility. A recent study
has shown that zinc oxide nanoparticles synthesized
biologically exhibit significantly higher biocidal activity
against various pathogens when compared to chemi-
cally synthesized ZnO nanoparticles\[2\]. Such prelimi-
ary studies suggest that biologically synthesized
nanoparticles have huge potential to address future
medical concerns. However, before putting these
nanoparticles into human healthcare actions, the key
step is to rule out their nano-toxicity and adverse effects
on long-term exposure. Therefore, efforts are required
to evaluate their pharmacology through conducting
dose dependent as well as time of exposure dependent
ex vivo and in vivo studies on human cell lines and
animal models. After successful evaluation of preclini-
cal efficacy and toxicity, nanoparticles showing favor-
able in vivo pharmacology response can be envisaged to
develop infection resistant composition of peritoneal
dialysis (PD) fluid. Simply, this will be achieved
through adding non-toxic doses of these nanoparticles
into different types of PD fluids widely used in clinics
and subsequently, evaluating (a) their efficacy against
variety of healthcare associated infections, (b) in vivo
adequacy, and (c) time stability to ensure their long-term
storage and prolonged shelf life. Strategically, a good start in this direction could be to evaluate the use of nano-sized particles of zinc oxide (ZnO) which is already listed as "generally recognized as safe (GRAS)" by the U.S. Food and Drug Administration (21CFR182.8991). Further more, various studies have shown that ZnO nanoparticles exhibit antimicrobial properties and is also used as food additive for its long-term preservation \[2\]. Likewise, the use of other antimicrobial nanomaterials safe to human beings (e.g. preferably Copper or Silver oxide NPs) can also be explored in the design of infection resistant PD fluid and further to bring the resulted composition into clinical use through performing meticulous translational research. Important to mention here is that the new PD fluid composition containing non-toxic doses of metallic nanoparticles would be delivered directly into the intraperitoneal cavity, therefore, intraperitoneal uptake of these nanoparticles to other parts of the body and thereof non-specific dissemination may lead to unexpected toxicities, side effects and other complications. Therefore, before putting the new PD fluid composition in clinical use, it would require careful assessment of its pharmacology and pharmacokineti cs.

In this regard, pharmacometabolomics, an emerging application of metabolomics for deriving early pre-clinical indications of efficacy and toxicity of pharmaceutical products, has huge potential to guide the anticipated translational research endeavors. Different from metal-based nano-particles, the use of nano-scale antimicrobial materials derived from natural biological substances, including oligo/poly-saccharide based nanoparticles, liposomes, dendrimers, and etc., can also be envisaged in this translational research endeavor. Further, the use of promising antimicrobial nanoparticles in conjunction with novel antibiotic agents can also be explored to manage multidrug resistant pathogens and formation of biofilms during long-term PD. The antibiotics can be added directly into the PD fluid containing antimicrobial nanoparticles at the time of intra-peritoneal instillation. Recently, Dr. Yang’s group and their collaborators from IBM Research have co-developed a biodegradable, biocompatible and cost-effective hydrogel that can adapt different shapes and can target variety of bacteria and fungi responsible for healthcare associated infections \[8\]. The remarkable property of these hydrogels is their ability to target multidrug-resistant biofilms and to
eliminate naturally by the body owing to their biodegradable nature. Therefore, these hydrogels could also serve as useful starting material in this endeavor i.e. to evaluate their clinically safe use for eradicating intraperitoneal, catheter exit-site and subcutaneous tunnel infections which are often caused by microbial adhesion and subsequent biofilm formation following episode(s) of infection.

In conclusion, necessity to improve the PD technology for limiting frequent PD associated infections and possibility to encompass the benefits of antimicrobial nanoparticles synthesized biologically, have been discussed in a translation research perspective. Particularly, the biocompatibility and cytotoxicity of metal based antimicrobial nanoparticles are the key issues to be addressed before putting them into clinical applications. I foresee that this perspective article would definitely appeal some of the biomedical researchers to put their conscience efforts in the direction of developing infection resistant PD fluid composition or nanotechnology based solutions targeting PD related biofilms for its efficient and long-term management.

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