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MICROPLASTICS: CLINICAL TRIALS PERSPECTIVES

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Abstract
Plastic pollution has emerged as one of the global challenges for the humanity. Plastics particles of millimeter and micrometer dimensions have been detected everywhere in the environment. Detection of tiny plastic particles in human blood and different organs has caused serious concerns and awareness in the society. Research activities have been initiated globally for better understanding the possible routes of entry and translocation of micro- and nano-plastics in human body. In vitro and in vivo studies have generated some primary data on these aspects. However, the major challenges in gathering data from clinical studies are lack of established methodology for designing ethically correct experiments, detection and identification of plastic particles and regulatory guidelines that needs to be designed specifically for micro- and nano-plastics. In this mini review article, readers are navigated through the recent updates on the clinical studies with microplastics and current challenges with some critical inputs.

Keywords
Microplastics, Clinical Trials, Placenta, Blood, IMTOX project, Regulatory Guidelines.

INTRODUCTION

Recent findings on the possible impact of microplastics (MPs) on human and environmental health have strongly suggested that MPs are already in the food chain and made entry to animal body including humans. This fate of MPs is perhaps one of the most unintended but serious consequences of environmental pollution that originates from anthropogenic activities. In this regard, it is pertinent to think that the globally recognized regulatory guidelines on plastic pollution have failed in all aspects. However, conclusive evidences of the fate of different MPs and interactive zone with animals are missing. The World Health Organization (WHO) has made some recommendations on the possible sources and monitoring of MPs in the drinking water. WHO in its report mentioned that routine monitoring of MPs in drinking water is not required and this was based on the lack of evidences to indicate a human health concern caused by MPs in drinking water (Marsden et al, 2019). From the regulatory point of view, such guidelines can be considered as the result of the findings of the majority of studies carried out across the globe. Talking about MPs pollution in general and making sense of the hazardous validity of MPs at cellular level are two different extremities of research domain. MPs are in air, water and earth and their final fate is determined by many biotic and abiotic factors. These aspects have been well explored with conclusive evidences (Das et al. 2021; Alimi et al. 2018). The recently developed interest in the research domain of MPs can be mostly attributed to the human health concerns reported by researchers from across the world. In particular, human physiological and anatomical presence of MPs has raised serious concerns in society. The unexpected discovery of MPs in human blood samples has proved that MPs are already in human body [Heather et al. 2022). This finding has actually opened new avenue of clinical research on MPs. This is of course a case where entry of MPs into human body was not under a clinical setting or voluntarily tested. A number of in vitro, in vivo and preclinical studies have been carried out by different research group on possible toxicity of MPs (Marko et al. 2021). A relevant question that arises is the availability and validity of clinical data of MPs based toxicity studies. Interventional or observational clinical studies with MPs are important for better understanding the possible health hazards at molecular level. However, administration of MPs to human participants is

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impractical and this is irrespective of the chemical composition, size, shape and surface properties of MPs. It is also obvious that data obtained from in vivo studies on the possible toxicity of MPs can not be extrapolated for clinical settings. A major challenge will be to establish the relationship between the variation in toxicity (acute or chronic) against the relevant changes in the dose and/or properties (size/shape/surface properties etc.) of a specific type of MPs under a clinical setting. In stark contrast, medical plastic engineering and manufacturing industries have revolutionized the biomedical application of plastics in the form of defect-free intelligent single use products under International Standard ISO 10993-1 safety regulations (Das et al. 2021). However, such regulation might not be applicable to MPs and this can be attributed to micro level size and changes in physicochemical properties of MPs. Some recent reports on the presence of MPs in human organ can guide clinical studies. The findings are indicative of exposure of MPs by ingestion or inhalation.

Some Case Studies of MPs of Clinical Significance

The case of Plasticenta

The first evidence of MPs in human placenta has been reported by Ragusa et al. In this study, vaginally delivered human placentas were collected from consenting women with physiological pregnancies and later analyzed for the presence of MPs (Ragusa et al. 2021). After Raman Microspectroscopy analysis of the samples, 12 fragments MPs of different sizes (5-10µm) were located in the fetal side, maternal side and the chorioamniotic membranes of the analyzed placentas. Chemical composition analysis of MPs showed them to be as stained polypropylene a thermoplastic polymer. Interestingly, around 3.8% (by mass) of the total mass (~600 g) of each placenta was only analyzed for each sample and this strongly suggested that total number of MPs within each placenta will be much higher. Presence of MPs in human placentas has raised two serious concerns regarding the possible roots of entry of MPs to the placental site and the possible consequences on pregnancy outcomes and foetus development. Respiratory and gastric organs were hypothesized as the sources of entry of MPs into blood stream and localization in the placental tissues. The study concluded that MPs may impart several adverse effects at cellular level during pregnancies. However, further studies are warranted to access if presence of MPs is harmful for pregnancies.

The case of placenta and meconium

Detection of MPs in human placenta and fetal meconium samples was reported recently (Braun et. al. 2021). A thorough protocol was developed under real-life clinical setting for the detection MPs. The placenta samples collected were from cesarean delivery and peripheral and central placental tissues were analyzed for the presence of MPs. Fourier-transform infrared (FTIR) analysis of the samples confirmed the presence of ten different types MPs including polyethylene, polypropylene, polystyrene and polyurethane within the size of 50µm. One of the significant finding of this study was the detection of MPs in the meconium samples that strongly suggested transplacental movement and ingestion of MPs to the fetus.

Some Ongoing Clinical Studies

Comparison of MPs levels in placenta and cord blood samples

Started in March 2022, this clinical trial has been undertaken for a comparative study of MPs levels in placenta and cord blood samples of pregnant women with fetal growth retardation (FGR) and healthy pregnant women (www.clinicaltrials.gov). The study will involve a total of 40 pregnant women. The methodologies are being optimized for the collection of blood sample from the vein of the umbilical cord and the maternal side of the placenta. The MPs extracted (if any) from the samples will be analyzed by µ-Raman spectroscopy for identification and quantification. The estimated completion date of this clinical study is March, 2023. The study will generate very important data on the possible role of MPs in causing FGR as compared to the control group.

MPs in ovarian and testicular tissue in humans

For the first time, a clinical study on the possible effects of MPs on human fertility and overall mammalian health has been initiated very recently (June, 2022) and expected to be completed within two years (www.clinicaltrials.gov). The study aims to generate data on the detection, identification and impacts of MPs in human granulosa cells and in the follicular fluid of women undergoing intracytoplasmic sperm injection (ICSI) treatment. In this observational type of clinical study, a total of 50 woman of above 18 years of age will participate. Raman spectroscopy and scanning electron microscopy will be used to analyze the samples for the detection of MPs.

The IMPTOX project

As a part of the European Research Cluster (CUSP) to understand the health impacts of MPs and nanoplatics (NPs) and under the European Union's Horizon 2020 program, the IMPTOX project in one of its objectives will specifically study the effects of environmental or dietary exposure to MPs and NPs on allergy and asthma using clinical studies in allergic schoolchildren living in cities and by the seaside (www. imptox.eu). Started in the last January, this projected is expected to be completed by February 2025. A total of 630 participants will be involved in this observational type clinical study. The expected outcome of this study is better understanding of the role of high concentrations of MPs and NPs in the environment and its link to the increased number of allergic people or worsens their allergies.

Current Challenges in Clinical Trials with MPs

Toxicity of MPs is being studied on animal model organisms belonging to different taxonomic groups. Most of the model organisms are of aquatic environment origin, while studies with freshwater and terrestrial organism are scanty at best (Marko et al. 2021). From safety and regulatory points of view, designing of interventional or observational clinical

studies with MPs is impractical. Routes of entry of MPs into human body and the mechanisms of their translocation to bloodstream and different organs first need to be investigated with animal studies. However, it will be difficult to extrapolate the data for clinical settings as biophysico-chemical properties of MPs might change significantly with the changes in volumetric changes in tested organ or tissues. In particular, absorption and distribution kinetics of MPs might differ significantly in human body as compared to other animals used for clinical testing. Overall, the obvious and immediate problem related to the clinical study of MPs seems to be the reverse data fitting or modeling obtained from the animal studies. As contrary to the common practices of clinical trials, ethically-designed experiments for interventional/observational/feasibility studies with MPs will need a different set of regulatory guidelines. With the existing regulatory guidelines, Absorption, Distribution, Metabolism and Excretion (ADME) studies for MPs are not feasible. Results from animal studies on the toxicity of MPs might be highly inconsistent predictors of toxic responses in humans. There are many reports on the limitation of extrapolating the average positive predictive value from animal to human tested for drug development (Gail, 2019). This necessitates the design of innovative experimental approaches for the clinical trials with MPs within the regulatory restrictions (Nuremberg code and Helsinki Declaration) of clinical trials (www.nih.gov; www.wma.net).

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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