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Editorial

Role of Di-2-Ethylhexylphthalate in Transfusion Medicine: Opportunities, Challenges and the Way Forward

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Transfusion medicine has advanced at a breakneck pace since Karl Landsteiner's discovery of blood groups at the turn of the last century. Glass bottles were the primary type of container used to collect blood from donors, but they were far from ideal. The bottles required cautious handling and storage since they were heavy and delicate. For reuse, they also needed to be cleaned and sterilized, and air bubbles that were caught in the rigid containers would make transfusions more difficult.

William Murphy and Carl Walter, two American scientists, developed the new plastic bags in the early 1950s. In 1963, the era of blood component therapy began when the FDA (United States Food and Drug Administration) finally certified the acid-citrate-dextrose (ACD) plastic blood bags following extensive clinical studies using the new plastic bags.[1] It was recommended to use a polyvinyl chloride (PVC) plasticized with di-2-ethylhexyl-phthalate (DEHP) since it can endure steam sterilization while remaining elastic and flexible. The purpose of the DEHP plasticizer was to soften and improve the usefulness of the hard PVC material. Plasticizers are fundamental for material flexibility in order to facilitate centrifugation, sealing, shipping, and regular handling of blood bags without running the danger of rupture and product loss.[2]

The new plastic bags took up approximately half as much room in a refrigerator as a glass container carrying the same quantity of blood, and they were lightweight, affordable, and unbreakable. They can also be made easily, kept sterile, and discarded after only single use. Compared to the previously employed glass bottles, polyvinyl chloride with DEHP has been used for more than five decades and has shown to be a dependable and durable technology that allows for significant advances in blood component quality, safety, storage, and transport. According to the World Health Organization, about 118.54 million blood donations are collected every year globally[3] and all of them in DEHP-PVC blood collection bags.

The surprising revelation that DEHP had a conservatory effect on erythrocytes, allowing for prolonged blood storage, increased the popularity of plastic bags.[4] Since then, studies have proved that DEHP improves RBC morphology in stored blood,[5] osmotic fragility[6] and microvesicle discharge without affecting the 2,3-DPG (2,3 diphosphoglyceric acid) and ATP levels.[7]

Although DEHP concentration in flexible polymer materials varies greatly, it typically ranges between 30% and 35% (w/w). DEHP is non-covalently bonded, lipophylic, and dissolved in PVC. DEHP may make about 30-40% of a standard blood collection bag based on weight. It is a key component of IV bags and tubing and is also used in nasal cannulas, oxygen masks, catheters, dialysis equipment, and a host of other medical devices.[8]

A big concern with DEHP is that it oozes out of blood collection bags and dissolves in fluid, i.e. blood, which then causes DEHP to enter the recipient's body during blood transfusion. DEHP is non-toxic at low concentrations. However, studies have noted adverse consequences in patients who require frequent blood transfusions, where a little quantity of DEHP begins to accumulate in their system after each transfusion and repeated transfusions may result in a high level of DEHP, resulting in adverse outcomes on the recipient's health.[9]

Complications related to the nervous system, the heart, and other organs have been noted in thalassaemia patients undergoing repeated transfusions of blood preserved in DEHP plasticized bags.[10]

According to a 1970 study, 5 to 7 mg of DEHP could be isolated from 100 ml of blood. In addition, two patients were found to have DEHP at levels ranging from 0.069 to 0.270 mg per gram dry weight of tissue.[11] According to a more recent analysis, the quantity of DEHP in RBC concentrates varied from 6.8 to 36.5 ug/ml as storage time increased. In comparison to RBC concentrates, irradiated red cell concentrates, fresh frozen plasma, and platelet concentrates, whole blood products showed the highest DEHP levels. It is established that DEHP has little to no impact on the quality of platelet and fresh frozen plasma concentrates.[12]

There has been a significant amount of research and discussion sparked by concerns about the possible toxicity of DEHP in humans. DEHP, recognized as a carcinogen in rats and mice,[12] is abundant in the environment. It caused testicular atrophy in rats given dietary doses,[13] and proceeded to lung injury in dogs and baboons administered with stored blood.[14]

Since DEHP is an endocrine disruptor and is categorized as being detrimental to reproduction (category 1B), its usage needs careful monitoring.[15] As a result, the use of DEHP in medical devices above 0.1% (w/w) is prohibited as of May 2025 under the Medical Device Regulation of the European Union (EU 2017/745 MDR).

Blood services and manufacturers are now exploring other plasticizer and storage options. The objective is to switch to non-DEHP blood collection and storage bags while retaining the blood bag set's physical properties and blood component quality.[16] Important factors to take into consideration include the toxicity of the DEHP alternative, the rate of leaching, and the effect on the physical properties of the blood bag set. Over the past ten years, a number of DEHP substitutes have been investigated; the most well-known ones include 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH), N-butyryl-n-hexyl citrate (BTHC), di(2-ethylhexyl) terephthalate (DEHT), and trioctyltrimellate (TOTM).[17,18]

However, studies have shown that the non-DEHP alternatives cause more haemolysis, necessitating a review of the RBC shelf-life.[19] To avoid the toxic effects of DEHP, it is pivotal to look for more sustainable alternative plasticizers. To guarantee safe blood transfusion, it is essential to understand how DEHP substitutes affect the numerous criteria (e.g. haemolysis, rate of leaching) linked to the preservation of blood and blood components. Since the banning of DEHP, blood services are facing a significant challenge that is still not completely addressed by the transfusion medicine fraternity.

In conclusion, to achieve a transition to an ideal non-DEHP product, a variety of plasticizer and storage solution options must be investigated. This transition will be a huge undertaking, involving significant time and financial commitments to support the enormous number of plasticizer/storage solution combinations to be tested. Collaboration on this front at the international level may prove to be critical.

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