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Does heated erythrocyte suspension transfusion with medical devices containing phthalates increase DEHP and MEHP levels?

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Abstract

Aims: It is commonly known that stored blood and blood products are heated before transfusion to prevent hypothermia, which leads to increased di-(2-ethylhexyl) phthalate (DEHP) content leaching into the blood and blood products and thereby causes greater conversion of DEHP to mono (2-ethylhexyl) phthalate (MEHP). However, there has been no study in the literature reporting on the amount of toxic phthalates in blood following the erythrocyte suspension (ES) transfused via warming. In this study, we aimed to investigate the DEHP and MEHP content in blood following the heated ES transfusions administered by DEHP-containing and DEHP-free infusion sets.

Methods: The study included 30 patients that were randomly divided into two groups with 15 patients each: group I underwent ES transfusion via DEHP-containing infusion sets warmed with blood-fluid warmers, and group II underwent ES transfusion via DEHP-free infusion sets warmed with blood-fluid warmers. DEHP and MEHP levels were measured both before and after transfusion.

Results: DEHP-free infusion sets led to no increase in the phthalate content, whereas DEHP-containing infusion sets significantly increased the DEHP and MEHP, where the DEHP level increased almost four times ($P = .001$).

Conclusion: DEHP-containing products lead to toxicity. Therefore, using DEHP-free medical devices may prevent toxicity in patients undergoing ES transfusion.

1 | INTRODUCTION

Blood-fluid warmers are commonly used in clinical practice, particularly in the emergency service and the operating rooms, for transfusing blood, blood products, and fluids by preventing the adverse effects of hypothermia. Line-type blood-fluid warmers are the most commonly used types since they are highly practical, inexpensive, and also do not require an additional kit for administration.[1-3] In Turkey, most medical devices such as blood infusion sets and blood bags are made of polyvinylchloride (PVC) that contain di-(2-ethylhexyl) phthalate (DEHP) as a plasticizer C. It is commonly known that DEHP leaches from the bag into the blood and blood products as a result of warming.[4,5] Moreover, DEHP converts to a more toxic metabolite known as mono (2-ethylhexyl) phthalate (MEHP) during the heating process.[4-6] It has been previously shown that exposure to DEHP-containing substances through inhalation or skin contact may result in gonadal injury or toxic effects on the reproductive system and kidneys.[2] It has also been recently reported that there is an association between exposure to DEHP and atopic dermatitis.[7] However, various harms of phthalate exposure have also been reported in human studies.[8-10]

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Literature indicates that although the DEHP content in blood stored in plastic bags has been extensively investigated, there has been no study reporting on the DEHP and MEHP content in blood following the erythrocyte suspension (ES) transfused via warming. Therefore, the present study aimed to evaluate the DEHP and MEHP content in blood following ES transfusions administered by commonly used DEHP-containing infusion sets and less commonly used DEHP-free infusion sets and also investigate whether the DEHP and MEHP content poses a risk factor.

What's known

Most of the blood bags are made of polyvinylchloride (PVC) containing di- (2-ethylhexyl) phthalate (DEHP). It also contains DEHP blood infusion sets in some countries, including Turkey. The transfusion by heating turns into MEHP, which is more toxic than other DEHP.

What's new

This study examines whether there is a difference between DEHP and MEHP levels between DEHP-containing sets and DEHP-free sets in heated erythrocyte suspension transfusions.

2 | MATERIALS AND METHODS

The study included 30 patients that were indicated for ES transfusion at Yuzuncu Yil University Medical School Emergency Service and Dokuz Eylul University Medical School operating rooms between December 2012 and May 2013. The study protocol was conducted in accordance with the 2000 revision of the Helsinki Declaration and was approved by the local ethics committee as named Yüzüncü Yıl University Clinical Research Ethics Committee. The patients were randomly divided into two groups with 15 patients each: group I included patients that underwent ES transfusion via DEHP-containing infusion sets (Braun, Melsungen AG) warmed with blood-fluid warmers (Eczacibası-Baxter, Istanbul, Turkey), and group II included patients that underwent ES transfusion via DEHP-free infusion sets warmed with blood-fluid warmers (Braun, Melsungen AG). Each infusion set was used for transfusing a maximum of two units. Blood samples were obtained from each patient both before and 5 minutes after transfusion, and DEHP and MEHP levels were analysed at Alfagen Laboratory. Yuzuncu Yil University Ethics Committee approved the study.

2.1 | Type and preparation of ESs

The whole blood is obtained with donations made in the blood banks of the centers where this study is designed and conducted. ES is obtained by subjecting it to various processes. First of all, the whole blood is centrifuged at 4000 rpm for 10 minutes. After the centrifugation process is completed, plasma accumulates in the upper part and erythrocyte in the lower part of the blood bag. The plasma portion of the blood that is accumulated at the top of the bag is transferred to another bag with the help of a fully automatic extractor.

A white layer of leukocyte platelets and some plasma leakage remains in between the erythrocyte and plasma. The white layer called buffy coat is thrown away into medical waste at the center of the study. The remaining erythrocyte-rich part is transferred to another bag consisting of a special leukocyte filter. It is then cleared of leukocytes, then 100 mL of SAG (saline, adenine, glucose) solution is added to it, and it is preserved for 42 days.

ES is stored in a blood storage box at +4°C. It is thought that there is no plasma remaining in the ES; it is assumed to be a negligible amount even if some part remains.

2.2 | Blood sampling and storing

Venous blood samples were collected from the brachial wing vein and were transferred to plain blood tubes. After centrifuging the tubes at 1200*g* for 10 minutes, the top serum layer was placed in DEHP-free Eppendorf tubes (Eppendorf AG, Hamburg, Germany) and stored at −80°C until biochemical analysis.

2.3 | Biochemical analysis

Serum DEHP and MEHP levels were measured using high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) technique.

2.4 | Statistical analysis

Statistical Package for the Social Sciences 21.0 package programme (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data are expressed as mean and standard deviation. The distribution of data was tested with Shapiro-Wilk. Parametric tests were used in statistical analysis since all the data belonging to the variables showed normal distribution. Paired *t*-test and independent *t*-tests were used for analysis. Before and after measurements of each group were compared using the paired *t*-test. Then the difference of the measurement value after the previous measurement was taken. The difference between independent groups was analysed by comparing these final values with the independent *t*-test. To evaluate the validation of the results and the accuracy, 10 000 random

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sampling with replacement bootstrap method was performed. Probability value of $P < .05$ was considered significant.[11]

3 | RESULTS

Tables 1 and 2 and Figures 1 and 2 present the pretransfusion and posttransfusion DEHP and MEHP levels in both groups.

The results indicated that pretransfusion DEHP and MEHP levels were highly similar to each other in both groups ($P < .05$) (Table 1 and Figures 1 and 2). However, posttransfusion DEHP and MEHP levels were significantly higher compared with their pretransfusion levels in the group administered with DEHP-containing infusion sets ($P < .0001$), and both levels were highly similar to their pretransfusion levels in the group administered with DEHP-free infusion sets ($P = .79$ and $P = .98$, respectively) (Figures 1 and 2). Table 2 showed the difference between posttransfusion and pretransfusion DEHP and MEHP levels with independent tests.

4 | DISCUSSION

Technology is currently advancing at a dazzling speed and thereby provides numerous facilities for human life. However, human life has become under serious threat since technology has led to the development of new chemicals and their products. The 2002 European Union Commission Report revealed that among the chemical substances in the world, there are 60 toxic substances that have been clearly shown to have serious hazards for the environment and humans.[8] One of these 60 substances is known as 'phthalate'. Phthalate is used as a plasticizer in numerous consumer products such as cosmetics, wallpapers, flooring materials, automotive industry, synthetic curtains, clothing, food packaging, toys, baby care products and medical devices.[9,10] As it provides elasticity and durability for these products, phthalate is produced in millions of tons worldwide and can result in human exposures by inhalation or oral or dermal contact.[12-15] DEHP is one of the most common forms of phthalate used as plasticizers.[16] MEHP, on the other hand, is the primary biodegradation product of DEHP. DEHP converts to MEHP through the lipase enzyme that is primarily available in the small bowel and pancreas and also in the liver, kidney, skin, lung and plasma.[17]

In light of the previous studies reporting on the toxic effects of DEHP, we performed ES transfusion after warming ES with blood-fluid warmers in order to avoid the risk of anaemia and also the hypothermic effects of ES and the side effects of ES such as acid-base imbalance. By doing so, we investigated the effects of normothermic ES transfusion on DEHP and MEHP in DEHP-containing and DEHP-free infusion sets warmed by blood-fluid warmers. The results indicated that DEHP and MEHP levels were not affected by the ES transfusions performed with heated DEHP-free infusion sets. In contrast, high amounts of DEHP leached from DEHP-containing infusion sets into the blood after warming, thereby leading to a significant increase in the MEHP levels resulting from DEHP metabolism.

Administration of acute blood loss in trauma patients and patients under anaesthesia is of vital importance for the survival of the patients. The recent trend of transfusing essential blood components instead of whole blood has led to the avoidance of numerous harmful effects of whole blood transfusion. Among these blood components, ES is currently the most common blood product used in the treatment of acute anaemia. To enable long-term preservation of blood products such as ES, the products are refrigerated at 4-6°C with the addition of various preservative solutions. Transfusion of ES prevents mortality and morbidity by enabling necessary oxygen for the tissues and by maintaining haemodynamic stability; however, blood-fluid warmers are needed to prevent the hypothermia caused by the transfusion of refrigerated ES.[18,19]

Nevertheless, it has been reported that blood-fluid warmers may lead to erythrocyte injury and increase DEHP toxicity because of the warming of the PVC product.[5] The rate at which DEHP leaches from the PVC product to the blood is dependent upon numerous factors, including the type of the plastic product and its temperature, storage time, the extent of shaking and the amount of DEHP in the PVC product. DEHP is highly lipophilic and does not chemically bind to the PVC polymer, and it also can easily leach into lipid-containing solutions when heated. Line-type blood-fluid warmers are the most common warmers used for heating blood products and fluids and are designed to deliver fluid sat 39°C to maintain normothermia.

TABLE 2 Analysis of differences in data between independent groups (mean ± SD)

	Group I (n = 15)	Group II (n = 15)	*P*
DEHP (μg/mL)[a]	3.0687 ± 0.51	0.0007 ± 0.14	<.001
MEHP (μg/mL)[b]	1.5533 ± 0.70	0.0100 ± 0.14	<.001

[a]Difference between posttransfusion and pretransfusion DEHP levels.
[b]Difference between posttransfusion and pretransfusion MEHP levels.

TABLE 1 Pretransfusion and posttransfusion DEHP and MEHP levels in both groups (mean ± SD) (min-max)

	Group I (n = 15)	Group II (n = 15)	*P*
DEHP[a] (μg/mL)	1.20 ± 0.28 (0.9-1.8)	1.21 ± 0.41 (0.5-1.9)	.97
DEHP[b] (μg/mL)	4.27 ± 0.41 (3.7-4.8)	1.21 ± 0.40 (0.5-2)	<.0001
MEHP[a] (μg/mL)	1.08 ± 0.37 (0.3-1.7)	1.11 ± 0.39 (0.3-1.7)	.80
MEHP[b] (μg/mL)	2.64 ± 0.72 (1.7-3.9)	1.12 ± 0.33 (0.4-1.7)	<.0001

[a]Pretransfusion.
[b]Posttransfusion.

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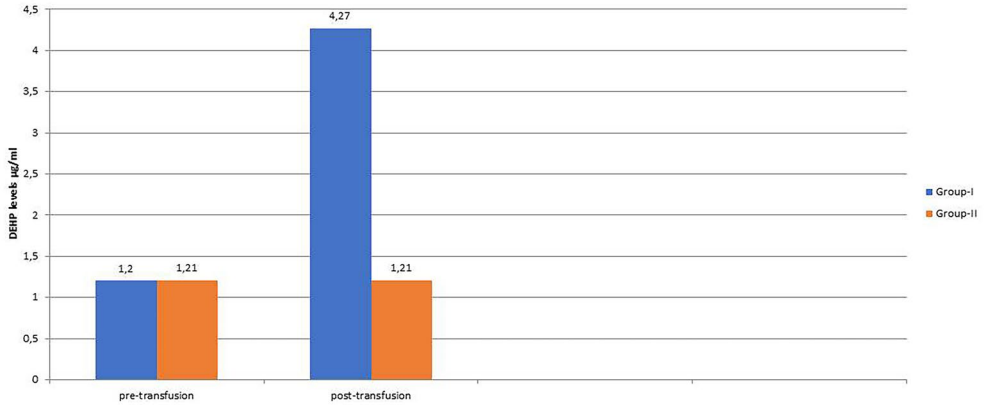


FIGURE 1 Comparison of pretransfusion and posttransfusion DEHP levels

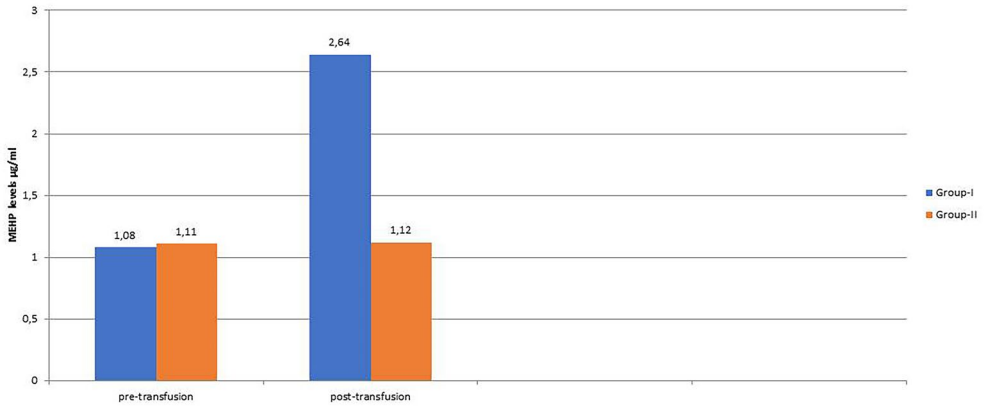


FIGURE 2 Comparison of pretransfusion and posttransfusion MEHP levels

The phthalates found in PVC products have low migration rates at low temperatures, but their migration rates increase with temperature, particularly at temperatures above 24°C.[21] In our study, DEHP and MEHP levels were not measured again in the following hours and days, and the patients were not observed in the long term. Therefore, the effect of high levels of DEHP and MEHP on toxicity is not fully understood.

Animal studies have indicated that exposure to DEHP may lead to harmful effects on the reproductive and endocrine systems.[21] Moreover, some other studies have reported that DEHP may have similar effects in humans and MEHP may have negative inotropic effects, decrease the concentrations of total T3 and free T4, and result in inflammation.[1,2,22] However, although the toxic effects of DEHP have been shown in animal models, there is insufficient evidence regarding the toxic effects of DEHP on humans. It is known that people who use plastic medical devices made of materials containing DEHP are exposed to certain degrees of DEHP, even for a limited duration. These exposures can sometimes be hundreds of times greater than those experienced by the general population. However, studies generally indicate that DEHP will be removed from the body within 24-48 hours and will not have long-term toxic effects.[5,23,24] However, there are hypotheses that mention the negative effects of DEHP and its metabolites, especially on the endocrine system and the male reproductive system.[1,23,25] The important points for toxicity in exposure is the medical procedure performed, the duration of administration, the young age group and body mass. Especially in premature newborns, total parenteral nutrition, exchange transfusion, extracorporeal membrane oxygenation, enteral nutrition in newborns and adults, heart transplantation or coronary artery bypass graft surgery and massive transfusion are procedural procedures that prolong exposure to DEHP.[23]

Phthalate has been associated with endocrine disorders in numerous epidemiological studies.[12] A longitudinal Taiwanese study extending over 12 years reported that prenatal exposure to phthalates might have negative effects on pubertal development.[26] Another study reported that plasma-free haemoglobin levels were 90.3 mg/dL after 35 days of storage in DEHP-containing plastic packs and 181.7 mg/dL in polyolefin bags, suggesting that the stability of red cells was lower in the DEHP-containing packs compared to DEHP-free packs[27] Leuenberger et al also revealed that DEHP was detected in urine samples on day 1 after the transfusion of autologous blood stored in DEHP-containing bags.[28]

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The most important limitation of this study is that no samples were taken from the patients for DEHP and MEHP measurement 24-48 hours later.

5 | CONCLUSION

The exact burden of blood bags, infusion sets and other plastic products on patients in emergency services, operating rooms and ICUs remains unknown. Our results indicated that DEHP-free infusion sets accumulate less in heated ES transfusions. Therefore, alternative infusion sets that can be relatively more costly, contain no plastic products such as polyethylene and polyurethane sets, can be preferred for ES transfusions. Although there are several studies in the literature reporting on the toxic effects of DEHP and MEHP, further larger studies are needed to investigate the acute and chronic toxicity caused by DEHP and MEHP. We believe that our results will provide guidelines for further studies.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of Yuzuncu Yil University, School of Medicine, Van, Turkey.

DISCLOSURES

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Gonullu E, Bilvanisi S and Gonullu H designed the study. Erkin Y, Aykac MC and Kume T performed the study and analysed the data. Gonullu E and Tasdogen A drafted the paper.

DATA AVAILABILITY STATEMENT

The analysed data sets generated during the present study are available from the corresponding author on reasonable request.

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