Reduction of exposure to plasticizers in stored red blood cell units

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Abstract

Introduction: Plastic can be toxic and hazardous to an organism's health, but it is being widely used in our daily lives. Di-2-ethylhexyl-phthalate is the most common plasticizer in medical devices made of polyvinylchloride and is commonly found in soft bags storing red blood cell units. Di-2-ethylhexyl-phthalate and its degradation product mono-2-ethylhexyl-phthalate can migrate into human body fluids, for example, blood and tissues. The aim of the study was to assess the concentration of plasticizers in red blood cell units according to storage time and after mechanical rinsing using a cell salvage device.

Methods: Levels of di-2-ethylhexyl-phthalate and mono-2-ethylhexyl-phthalate were analysed in 50 unwashed red blood cell units using liquid chromatography coupled with tandem mass spectrometry. In addition, phthalate concentrations were measured before and after mechanical rinsing in six more washed red blood cell units with storage times ranging between 36 and 56 days. A linear regression model was determined by the daily increase of di-2-ethylhexyl-phthalate and mono-2-ethylhexyl-phthalate in the stored red blood cell units subject to their storage time (range = 4–38 days), and the effect of mechanical rinsing on their phthalate concentration was calculated.

Results: A linear correlation was found between storage time of unwashed red blood cell units and the concentration of di-2-ethylhexyl-phthalate ($p < 0.001$) or mono-2-ethylhexyl-phthalate ($p < 0.001$). Stored red blood cell units older than 14 days had significantly higher concentrations of both contaminants than red blood cell units of shorter storage time ($p < 0.001$). Mechanical rinsing in washed red blood cell units attained a reduction in the di-2-ethylhexyl-phthalate and mono-2-ethylhexyl-phthalate concentration by a median of 53% (range = 18–68%; $p = 0.031$) and 87% (range = 68–96%; $p = 0.031$), respectively.

Conclusion: Leaching of di-2-ethylhexyl-phthalate and mono-2-ethylhexyl-phthalate into red blood cell units depends on the duration of storage time. Plasticizers can be significantly reduced by mechanical rinsing using cell salvage devices, and thus, red blood cell units can be regenerated with respect to chemical contamination.

Keywords

plasticizers; red blood cell units; mechanical rinsing; storage time; di-2-ethylhexyl-phthalate

Introduction

Plastic is made flexible by the addition of plasticizers. Di-2-ethylhexyl-phthalate (DEHP) is the most prevalent synthetic polymer softener in medical devices and

is almost exclusively used in stored bags for red blood cell units (RBCUs). Particularly during invasive treatment, when used to deliver enteral or parenteral lipophilic fluids (i.e. blood), leaching of DEHP and its degradation product mono-2-ethylhexyl-phthalate

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(MEHP) into the recipient's circulation and its deposition in human tissue have been frequently attested.¹⁻⁸

In the last decades, considerable concerns regarding the side effects of plasticizers on endocrine, testicular, ovarian and neural function, as well as their hepatotoxic and cardiotoxic impact have been raised.⁹⁻¹¹ The distribution of phthalates and other plasticizers is being regulated by the European Union (EU).¹² Surprisingly, although DEHP and five other phthalates are now forbidden in the manufacturing of children's toys, the use of phthalates in medical products is still permissible.¹³

Cell salvage devices are used during surgical procedures in order to collect and recycle autologous blood. Collected blood components are separated into its constituents according to their weight by centrifugal force and washed with a 0.9% saline solution. Erythrocytes are pressed to the outer wall of the preparation bowl, and with increasing centrifugal speed, the low mass blood components are aspirated in the middle. The elimination rate of anticoagulation solutions, free haemoglobin and potentially dangerous substances ranges from 75% to over 90%.^{14,15} This results in a purified product of concentrated autologous erythrocytes suspended in normal saline. However, to date, it is unknown in which way plasticizers in RBCUs can be diminished by mechanical rinsing using a cell salvage device.

The aim of the study was to measure the content of DEHP and MEHP in stored unwashed RBCUs and to explore the reduction of these contaminants in washed RBCUs by cell salvage application.

Methods

Storage conditions for RBCUs

A total of 56 leucocytes-reduced RBCUs, preserved in saline-adenine-glucose-mannitol solution (SAG-M), were obtained from the Institute for Transfusion Medicine (Suhl, Germany). All units were handled according to German guidelines for the collection of blood and blood components.¹⁶ The manufacturer performed leucocytes reduction of whole blood or buffy coat-reduced RBCUs after separation into components by inline filtration on the collection day, or the day after, at the latest 22 hours after donation. All RBCUs were stored at 4°C immediately after preparation. On Day 2 or Day 3 after collection, all RBCUs were shipped to our institution. Thereafter, RBCUs were stored at +4°C ($\pm 2^\circ\text{C}$) in a refrigerator (Kirsch, Offenburg, Germany). Cold storage was only interrupted to obtain samples for cross-matching.

Plasticizers in unwashed RBCUs

In total, 50 stored RBCUs were analysed before being transfused to patients. Storage times for application of

each RBCU were documented in the study protocol. Blood samples (5 mL) were stored at -20°C in glass vials. Stored blood samples were analysed for the plasticizers DEHP and MEHP. The analytical determination was performed using liquid chromatography coupled with tandem mass spectrometry according to a previously published analytical method.^{17,18} The limits of quantitation (LOQ) for DEHP and MEHP were 5 and 2 $\mu\text{g/L}$, respectively. The content of DEHP and MEHP in RBCUs was determined depending on storage time.

Plasticizers in washed RBCUs

Six additional stored RBCUs were intentionally chosen according to the longest storage time (median = 37 days, range = 36-56 days) in order to obtain RBCUs with higher levels of DEHP and MEHP. The recovery and storage of the RBCUs is similar to the above guidelines.¹⁶ A standard cell salvage machine (Elektta; Sorin Group®) fitted with a 175-mL washing bowl was filled with 300 mL of donor blood (RBC) at a rate of 250 mL/min centrifugal speed.¹⁵ After filling the bowl, the rinsing programme started automatically using 600 mL of physiological saline solution (NaCl 0.9%, 'phthalate-free') and a pump rotation speed of 350 mL/min. The 'washed RBCUs' were transferred into a new plastic bag at a rate of 200 mL/min pump rotational speed. Blood samples (5 mL) were taken before and after mechanical rinsing, respectively, and stored in glass vials until analysis. Accordingly, levels of DEHP and MEHP were measured as stated above.

Theoretical model to illustrate patient stress

A statistical linear regression model was determined by the daily increase of DEHP and MEHP in unwashed RBCUs. Accordingly, phthalate concentrations were calculated according to the storage time. Important toxic outcomes of DEHP also resulted from adverse effects of its degradation product MEHP, which stresses a joint assessment of both compounds. Therefore, to assess the total burden of plasticizers in RBCUs, the DEHP equivalent (DEHP_{eq}) calculation is needed due to the different molecular masses of DEHP and MEHP. Molecular weights ($\text{DEHP} = 390.56 \text{ g/mol}$ and $\text{MEHP} = 278.35 \text{ g/mol}$) were set in proportion to obtain the conversion factor

$$\frac{390.56 \frac{\text{g}}{\text{mol}}}{278.35 \frac{\text{g}}{\text{mol}}} = 1.403$$

To calculate DEHP_{eq} , the following formula was used

$$\text{DEHP}_{\text{eq}} = \text{DEHP} [\text{mg/L}] + 1.403 \text{ MEHP} [\text{mg/L}]$$

Figure 1. Linear regression between storage time of 50 RBCUs and DEHP or MEHP concentrations.

The tolerable daily intake (TDI) level indicates the amount of the daily intake of a product at which no adverse effects on health have to be expected. For safety, TDI levels are set by dividing the ‘No Observed Adverse Effect Level’ found in animal studies with an adjustment factor of 100. In case of DEHP, the TDI is 50 mg/kg body weight.^{9,19,20}

Patient stress by phthalate contamination and the effect of mechanical rinsing were calculated for a 5-kg child. Calculations included the following:

1. The content and exposure to DEHP_{eq} after administration of 100-mL unwashed RBCUs.
2. The calculated total burden of plasticizers (DEHP_{eq}) was related (%) to the TDI of DEHP. The allowed TDI of DEHP (0.05 mg/kg body weight) in a 5-kg child is 0.25 mg.
3. The effect of mechanical rinsing on reducing the total burden of plasticizers was calculated after administration of 100 mL of washed RBCUs when compared to unwashed RBCUs.

Statistics

The data are expressed as mean $\pm$ standard deviation (SD) with 95% confidence interval (95% CI). The correlation between storage time (days) of 50 RBCUs and their content of DEHP and MEHP was calculated using Pearson’s correlation method. To identify a threshold of storage time, we divided the RBCUs into two groups depending on their content of plasticizers. In the following, two conditional inference trees²¹ using depth one (only one branch) were modelled with regard to time, MEHP and DEHP as independent variables. Threshold values were determined by the trees as cut-off points. Significance between groups was calculated by the non-parametric Mann–Whitney U test or *t*-test, according to

distribution. To examine the difference between content of DEHP and MEHP in RBCUs before and after mechanical rinsing, a Wilcoxon signed-rank test was used. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were conducted using the software R version 3.3.0 (R Foundation for Statistical Computing).

Results

Unwashed RBCUs

The 50 RBCUs were received from the blood bank between 4 and 38 days after preparation. Median storage time of RBCUs was 8 days. The DEHP and MEHP levels in the RBCUs ranged between 5.3–38.1 mg/L (median = 13.0 mg/L) and 0.8–14.8 mg/L (median = 1.4 mg/L), respectively. A significant correlation was found between storage time of RBC and the DEHP (Pearson = 0.730; $p < 0.001$) and MEHP (Pearson = 0.730; $p < 0.001$) concentrations (Figure 1).

RBCUs stored for less than 14 days had significantly lower DEHP and MEHP concentrations than RBCUs stored for a longer time ($p < 0.001$). In RBCUs stored for less than 14 days ($n = 31$ /median = 7 days), DEHP and MEHP levels were 11.0 ± 4.2 mg/L (95% CI = 9.6, 12.5) and 1.3 ± 0.5 mg/L (95% CI = 1.2, 1.5), respectively. In RBCUs stored for ≥ 14 days ($n = 19$ /median = 24 days), DEHP and MEHP levels were 21.7 ± 7.4 mg/L (95% CI = 18.4, 25.1) and 5.3 ± 3.4 mg/L (95% CI = 3.7, 6.9), respectively (Figure 2).

Washed RBCUs

In RBCUs used for cell salvage processing ($n = 6$), the average storage time was 31.2 ± 8.8 days. After the mechanical rinsing through the cell salvage device, levels of DEHP and MEHP were found to be significantly

Figure 2. DEHP and MEHP release into 31 RBCUs stored for <14 days versus 19 RBCUs stored for ≥14 days.

Figure 3. Reduction of DEHP and MEHP before and after mechanical rinsing of six RBCUs.

lower when compared to baseline levels (DEHP at baseline = 40 ± 14 mg/L (95% CI = 27, 52) versus DEHP after mechanical rinsing = 18 ± 2 mg/L (95% CI = 17, 19); $p = 0.031$ and MEHP at baseline = 9 ± 6 mg/L (95% CI = 4, 14) versus MEHP after mechanical rinsing = 1 ± 0.7 mg/L (95% CI = 0.5, 1.6); $p = 0.031$). Thus, cell salvage processing attained a reduction in the DEHP and MEHP content by a median of 53% (range = 18–68%; $p = 0.031$) and 87% (range = 68–96%; $p = 0.031$), respectively (Figure 3).

Theoretical model

The TDI level in a 5-kg child was overcome three-fold after administration of 100-mL untreated RBCUs at Day 1 of storing and was increased 14.8-fold after

38 days of storing. In washed RBCUs, the TDI from DEHP_{eq} would be reduced by 1.5–5.6 according to storage time (Table 1).

Discussion

All tested RBCUs used in this study contained the plasticizer DEHP as well as its degradation product MEHP. Levels of both compounds increased significantly when the storage time was longer, particularly after 14 days. A phthalate contamination of RBCUs, as well as its association with storage time, has been previously described by other groups.^{7,22,23} Compared with these, phthalate levels found in this study were somewhat lower than reported, which may indicate an improvement of product quality during the last decade. Nevertheless, the

Table 1. Calculated content and exposure to plasticizers after administration of 100-mL unwashed and washed RBCUs in a 5-kg child.

Storage time (days)	1	7	14	28	38
Unwashed RBCUs					
DEHP _{eq} (mg/100 mL)	0.82	1.4	1.9	3.0	3.7
Increase of TDI ^a (%)	330	540	760	1,180	1,480
Washed RBCUs					
DEHP _{eq} (mg/100 mL)	0.38	0.57	0.75	1.13	14.0
Reduction of DEHP _{eq} by mechanical rinsing (%)	54	58	60	62	62
Reduction of TDI by mechanical rinsing ^a (%)	150	230	300	450	560

RBCUs: red blood cell units; DEHP: di-2-ethylhexyl-phthalate; TDI: tolerable daily intake.

^aAllowed TDI of DEHP (0.05 mg/kg body weight) in a 5-kg child is 0.25 mg.

persistent exceedance of the TDI for DEHP may be still a cause of concern for health effects and should be avoided if alternative solutions exist.

Storage of RBCUs is associated with an almost complete loss of 2,3-diphosphoglycerate within 2 weeks and increasing signs of cell damage, for example, cell degradation, changes in electrolyte balance, particularly the release of potassium, increased levels of lactate and citrate and deformation of erythrocytes. Particularly in infants and toddlers, storage time of RBCUs should be kept short in order to reduce the exposure of erythrocytes to phthalates.²⁴

Mechanical rinsing of stored blood aliquots is commonly used prior transfusion in order to clean them from exceeding electrolyte imbalances.²⁴ A reduction of potassium and lactate levels by 94% and 99%²⁵ and restoration of sodium levels, from 93 to 140 mmol/L, have been reported.²⁶

To our knowledge, this is the first study evaluating the effect of mechanical rinsing on phthalate concentration in RBCUs. By employing a cell salvage device, we found a reduction of both DEHP (53%) and MEHP (87%) in washed RBCUs, which implies that the exposure of these contaminants to patients can be reduced effectively. The impact was more pronounced with higher initial phthalate concentrations prior washing. However, a considerable amount of plasticizers may remain, which should be avoided particularly in highly vulnerable patients, for example, neonates.

Particularly in the treatment of premature neonates and newborns, the long-standing effect of phthalates on fertility should not be underestimated, and the awareness of a potential phthalate intoxication should be raised.^{9,27} The recommended maximum TDI of DEHP is 50 µg/kg body weight.⁹ By the combination of a short storage time (maximum 7 days) and mechanical rinsing, the exceedance of the recommended TDI can be reduced remarkably from 14.8-fold to 2.3-fold when administering a quantity of 100 mL of RBCs in a 5-kg infant. As a consequence of these results, it is worth considering whether it would be pertinent to use blood products

that have been rinsed by mechanical means on the day of surgery, or indeed within a few hours of use, particularly for neonates and infants who are expected to need packed red cell transfusions:

‘The U.S. Food and Drug Administration (FDA) and European Commission advocate abolition of DEHP for all products in contact with high risk groups such as children before the onset of puberty, and suggest that alternative materials without any relevant detrimental effects be used, if they exist, in order to minimize health risks from products containing DEHP.’^{27,28}

There are many alternatives to replace the common plasticizers in RBCUs. The European Commission specifies tri-(octyl) trimellitate (TOTM) as an alternative plasticizer for stored RBCs, which is included in the ‘List of Additives’ in the Synoptic document no. 7 of the European Commission ref. no 94800.^{9,29} It is less harmful for patients, staff and the environment. Moreover, recent studies demonstrated the considerably slower migration of TOTM into blood compared to DEHP.^{2,19,30} Other good alternatives like silicone and polyurethane, which are widely used for platelet and plasma storage bags, have critical financial implications for producers of whole blood bags.³¹ RBCUs stored in bags plasticized with 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) could be an alternative to bags releasing DEHP as well.³² However, concerning the membrane stabilizing effect of DEHP, these alternatives such as poly-(ethylene-co-ethyl acrylate) (EEA) do not currently show the same quality regarding the stability of the erythrocyte membrane during long-term storage.^{31,33–35}

Limitations

Measurements of unwashed and washed RBCUs were consecutive in different settings. Hence, equal groups would have been more conclusive.

Conclusion

In conclusion, this study demonstrates that the burden of phthalate concentrations in RBCUs can be effectively reduced by shortening the storage time and by mechanical rinsing. The legal regulations of the European Commission for minimizing the risks from medical products containing DEHP and other plasticizers demand the relegation of risks from the use of medical products containing DEHP.⁹ Cell salvage of RBCUs allows one to fulfil these demands. Alternatively, manufacturers of medical devices could rethink producing phthalate-free single-use materials in the long term.

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