

## ARTICULO

**Association between appropriate use of transfusion in children and in-hospital mortality: a Venezuelan prospective cohort study.**

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## RESUMEN

**Asociación entre el uso apropiado de transfusión en pediatría y mortalidad intra-hospitalaria: Estudio de una cohorte prospectiva venezolana.**

Los riesgos de la transfusión han sido estudiados extensamente; sin embargo, información relacionada con el uso apropiado de la transfusión en pediatría y mortalidad intra-hospitalaria se desconoce. El objetivo fue determinar la asociación entre el uso apropiado de transfusión en pediatría y la mortalidad intra-hospitalaria. Se diseñó una cohorte prospectiva. Para evaluar el uso apropiado se utilizaron los criterios de la "American Association of Blood Bank Pediatric Hemotherapy". Se realizó en el Hospital Infantil "Dr. Jorge Lizarraga", Valencia, Venezuela, entre enero de 2002 y septiembre de 2003. El principal desenlace fue muerte durante la hospitalización. 617 pacientes (< 15 años, masculinos = 57%) fueron evaluados. El uso apropiado fue 81.2% (501/617). En el grupo de transfusión no apropiada, la tasa de incidencia (TI) de mortalidad fue 7 por 1000, mientras que en el grupo de transfusión apropiada la TI fue 3,6 por 1000. La razón de TI fue 1,98 (IC95% = 1,1 a 3,6, p = 0,01). El hazard ratio (HR) crudo fue 2 (IC95% = 1,2 a 3,5 p = 0,01). Al analizar el efecto del uso no apropiado sobre la mortalidad en los distintos grupos de edad, hubo un mayor efecto en los mayores de 1 año (HR=4,4, IC95% = 1,39 to 13,6 p = 0,01) comparado con el efecto en los menores de 1 año (HR= 1,5 IC95%= 0,79 to 2,9, p = 0,2). Conclusión: La transfusión inapropiada de pacientes pediátricos hospitalizados se asocia con un incremento de riesgo de muerte. Todo esfuerzo educacional sobre el uso apropiado de la transfusión es loable. Se requieren más estudios que evalúen la asociación entre la transfusión y mortalidad.

**Palabras clave:** Mortalidad, transfusión, uso apropiado, pediatría.

## ABSTRACT

**Association between appropriate use of transfusion in children and in-hospital mortality: A Venezuelan prospective cohort study.**

Blood transfusion risks have been studied extensively, but data regarding appropriate use of transfusion and survival on hospitalized children are unknown. The purpose of this study was to determine the association between appropriate use of transfusion in

children and in-hospital mortality. It was a prospective cohort study. Appropriateness of blood transfusion was evaluated using American Association of Blood Bank Pediatric Hemotherapy. This research was carried out in "Dr. Jorge Lizarraga", Children's Hospital Valencia, Venezuela from January 2002 until September 2003. The main outcome measure was death during hospitalization. 617 children (< 15 years old, male = 57%) were evaluated. Appropriateness was 81.2% (501/617). For non appropriate transfusion group, incidence rate (IR) of in-hospital mortality was 7 per 1,000 while IR for appropriate transfusion group 3.6 per 1,000; IR ratio was 1.98 (95% CI= 1.1 to 3.7, p = 0.01). Crude hazard ratio (HR) was 2 (95% CI = 1.2 to 3.5). In patients > 1 year old, HR was 4.4 (95% CI = 1.39 to 13.6, p= 0.01); in patients < 1 year old, HR was 1.5 (95% CI = 0.79 to 2.9, p = 0.2). Conclusion: Inappropriate transfusion in hospitalized children is associated with an increased risk of in-hospital mortality. Educational efforts addressing appropriate use of blood component should be increased. Further studies about association between transfusion and mortality are needed.

**Key words:** In-hospital mortality, appropriateness, transfusion, children.

## INTRODUCTION

Blood transfusion has been associated with a number of adverse outcomes (1-4) that include infections (5-10), transfusion-associated graft-versus-host disease (11-13), massive transfusion-related mortality (14), transfusion-related acute lung injury (15-17), transfusion-induced liver disease (18), transfusional iron overload (19), transfusion-related sepsis (20), anaphylactic transfusion reactions (21), post-transfusion purpura (22), transfusion-related multiple organ failure (23), and transfusion-related immune modulation (24). Even blood transfusion was found to be associated during or after coronary artery bypass operations with increased long-term mortality (25). However, the majority of studies made in transfusion medicine have not supplied information about the impact of appropriate use of blood component on mortality. This paucity of reports regarding this association makes it difficult to draw meaningful conclusions in this very important clinical issue.

In a cross sectional study about appropriate use of transfusion in pediatric patients, Martí et al (26) determined appropriateness of 60.9%. So, it would be important to evaluate whether there is any association, and to what extent, between appropriate use of transfusion in this population and risk of in-hospital mortality. As far as we know, there have been no studies that specifically address this research question. To answer this, we undertook a prospective cohort study.

## METHODS

**Study Sample.** Our prospective cohort was restricted to pediatric patients (< 15 years old) who required to be transfused for any disease while hospitalized at the "Dr. Jorge Lizarraga Hospital" in Valencia, Venezuela. The period of study was from January 2002 to September 2003.

The exposure variable was appropriate use of transfused blood component at any point during their hospitalization; American Association of Blood Bank Pediatric Hemotherapy Committee Guidelines for Auditing Pediatric Transfusion Practices (27) was used to evaluate the appropriateness of blood transfusion. The outcome of interest in this study was in-hospital mortality, which we defined as deaths that occurred during hospitalization. The following covariates were considered: age, gender, hospitalization section, blood component or whole blood, and type of diagnosis (medical or

surgical). This research was approved by the Ethical Committee of the Ciudad Hospitalaria “Dr. Enrique Tejera”.

**Statistical analysis.** We evaluated the association between the appropriate use of transfusion and in hospital mortality by means of chi square analysis. Kaplan-Meier survival curves were plotted to evaluate death in hospital among appropriate use and non-appropriate groups. To determine whether the difference between in-hospital death in the two groups was significant, we applied the Mantel log-rank test. The proportional hazards regression model was used to derive unadjusted and adjusted hazard ratios for in-hospital death. Adjusted hazard ratios were derived by loading all the variables that were considered to be potential confounders into the model.

The initial model was composed by in-hospital mortality as the outcome variable, inappropriate transfusion as the exposure variable, and age, gender, type of blood component, type of diagnosis (medical or surgical), as potential confounders. Model evaluation was done using likelihood ratio test. All reported P values are two-sided, with a type 1 error rate fixed at 5%. Stata software (version 8.0, Stata, College station, Tex.) was used for analysis of results.

**RESULTS**

General. 617 children (< 15 years old, male = 57%) were evaluated. General characteristics are shown in Table 1, respectively. Mean time of hospitalization before-after transfusion, and overall is shown in Table 2.

**Table 1.** General characteristics of patients, transfusion and outcome

Variable	n	%
<b>Gender</b>		
▪ Male	352	57.0
▪ Female	265	42.9
<b>Blood component</b>		
▪ PRC	430	69.9
▪ Whole blood	15	2.4
▪ Platelet	55	8.9
▪ FFP	106	17.1
▪ Cryoprecipitate	5	0.8
▪ Albumin	6	0.9
<b>Appropriateness</b>		
▪ Yes	501	81.2
▪ No	116	18.8
<b>In-hospital mortality</b>		
▪ Yes	61	9.8
▪ No	556	90.1

*PRC = Packed red cell FFP = Fresh frozen plasma*

**Table 2.** Days of hospitalization before-after transfusion (P<sub>25</sub>, Median, P<sub>75</sub>)

Hospitalization (days)	Median (IR)
Prior transfusion	2 (1 to 6)
After transfusion	12 (7 to 22)
Overall hospitalization	18 (10 to 29.5)

*IR = interquartile range*

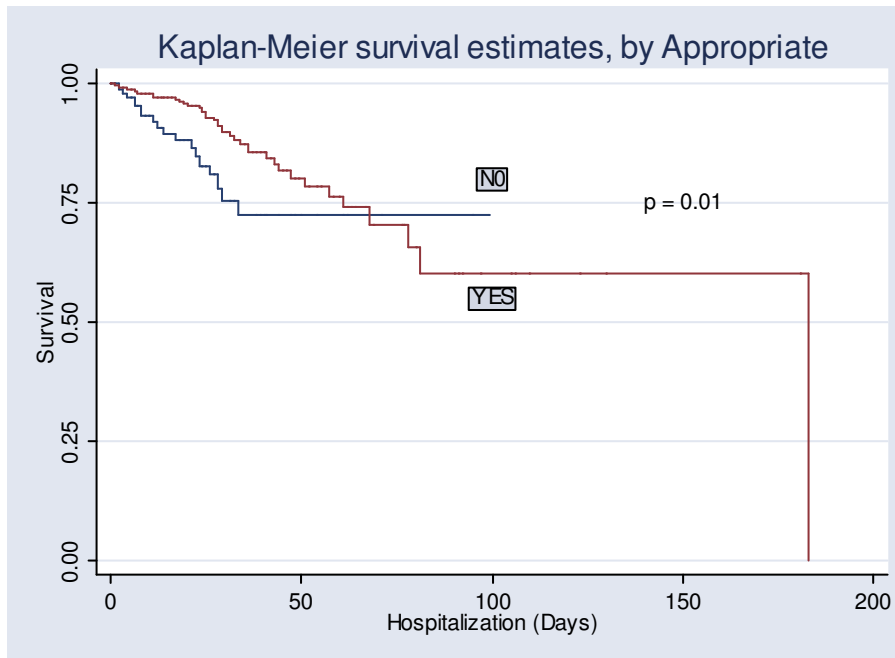
Age distribution by age was as follows: less than 8 days old (n = 187 [30.1%]), between 8 and 30 days old (n = 119 [19.2%]), between 31 and 365 days old (n = 100 [16.2%]), and more than one year-old (n = 211 [34.2%]). Appropriateness was 81.2% (501/617). Appropriateness of transfusion by blood component is shown in Table 3.

**Table 3.** Appropriateness of transfusion by blood component

Outcome	Appropriateness (n =501 [81.2%])						Non-appropriateness (n=116 [18.8%])				
	Blood component						Blood component				
	PRC	P	FFP	Cy	WB	Alb	PRC	P	FFP	Cy	WB
<b>Death</b>	27	8	6	1	1	---	8	3	7	---	---
<b>(n= 61)</b>	(7.5)	(18.6)	(7.7)	(50)	(7.7)		(11.3)	(25)	(25)		
<b>Alive</b>	332	35	72	1	12	6	63	9	21	3	2
<b>(n=556)</b>	(92.4)	(81.3)	(92.3)	(50)	(92.3)	(100)	(88.7)	(75)	(75)	(100)	(100)
<b>Total</b>	359	43	78	2	13	6	71	12	28	3	2
<b>(n= 617)</b>	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

*PRC = Packed Red Cell; P = Platelet ; FFP = Fresh Frozen Plasma;  
Cy = Cryoprecipitate; WB= Whole Blood; Alb = Albumin*

**Survival and appropriateness.** For non appropriate transfusion group, incidence rate (IR) of in-hospital mortality was 7 per 1000 while IR for appropriate transfusion group 3 per 1000. IR ratio was 1.98 (95%CI = 1.1 to 3.6, p = 0.01). Survival curves by use appropriateness are shown in figure 1.



**Figure. 1** Survival curves by appropriate use of transfusión

Crude evaluation of association between mortality and transfusion showed a hazard ratio (HR) of 2 (95%CI = 1.2 to 3.5). An interaction or effect modification was detected between the inappropriate use of blood component and age.

When analyzing the effect of inappropriate use on mortality in different age groups, a greater effect in patients > 1 year old (HR=4.4, 95%CI 1.39 to 13.6 p = 0.01) than patients < 1 year old (HR-1.5 (95% CI = 0.79 to 2.9, p = 0.2) was observed. See tables 4 and 5.

**Table 4.** Final model of association between inappropriate transfusion and in-hospital mortality for patients > 1 year old (n = 211).

Variable	HR	95%CI	P
Inappropriate transfusion	4.3	1.39 to 13.6	0.01
Gender	0.6	0.1 to 1.81	0.3
PRC	0.2	0.07 to 0.6	0.008
Platelet	0.4	0.08 to 2.2	0.3

HR=Hazard ratio; PRC = Packed red cell; 95%CI = 95% Confidence Interval

**Table 5.** Final model of association between inappropriate transfusion and in-hospital mortality for patients <1 year old (n = 406).

Variable	HR	95% CI	P
Inappropriate transfusion	1.5	0.79 to 2.9	0.2
Gender	0.9	0.5 to 1.8	0.9
PRC	1.0	0.4 to 2.3	0.9
Platelet	1.1	0.4 to 3	0.7
Surgical diagnosis	2	1 to 4	0.05

*HR=Hazard ratio; PRC = Packed red cell  
95%CI = 95% Confidence Interval*

Comparison of survival curves by blood component group and gender showed a nonstatistical significance difference (log-rank test, p=0.47 and p=0.75 respectively).

### DISCUSSION

Recently, Murray and Roberts wrote “Sick neonates are one of the most heavily transfused groups of patients in modern medicine. However, despite considerable research, most neonatal transfusion practice remains opinion based rather than truly evidence based. Most neonatologists would not prescribe drugs to their patients unless there was a reasonable expectation of benefit. Unfortunately, this rigor does not translate to the prescription of blood products, and as a result there exists a diversity of opinion and practice among different clinicians and institutions” (28). Our data indicate a high risk of in-hospital mortality in pediatric patients exposed to inappropriate blood transfusion.

What mechanisms could explain these findings? First, stored red blood cells selectively activate human neutrophils leading to the release of IL-8 and secretory phospholipase A2, and provoking multiple organ failure (29). It has been suggested that the age of red blood cells (RBC) at transfusion is a factor in transfusion-associated morbidity and mortality (30-31). Unfortunately, our study was unable to collect data about the blood collection day. Secondly, another mechanism might be allogeneic blood transfusion (ABT)-induced postoperative bacterial infection (PBI) (32-34), through transfusion-induced immunosuppression (35-36).

Whatever the cause of transfusion-related poor outcomes, there is a need to enhance the safety profile associated with transfused whole blood or its component, which has led toward a movement to improve the appropriate use of ABT (37).

Given the potential adverse effects of transfusions, it is necessary to understand their effectiveness in order to reduce blood component utilization

(38). Currently, at the era of the Evidence-based Public Health (39-40), transfusion therapy assumes an understanding of the natural history of disease; so, any physician who makes the decision of transfusing a sick child must be trained in knowing transfusion guidelines for neonates and older children (41); this would help to reduce adverse outcomes when a transfusion is indicated (42). It is knowledge as evidence-based transfusion practice (43) or evidence-based practice of transfusion medicine (44). All this is related to one of the fundamental goals of public health: preventing disease in order to reduce human suffering (45).

We believe this study may have two limitations, and therefore its results must be interpreted accordingly. First, there is a possibility of selection bias in the process of data gathering. However, we consider that the fact of having discovered a modification effect decreases the likelihood of such a bias. Besides, in this research all patients were followed up until outcome developed. Secondly, we could not determine any plausible mechanism to explain why age modifies the effect of inappropriate use on mortality. Unfortunately, there are no other similar studies to compare these results. As far as we know, this is the first study of this type being conducted worldwide.

**Conclusion.** Appropriate transfusion in children did appear to reduce the risk of in-hospital mortality in this population. Educational efforts addressing appropriate use of blood components should be increased. Further studies are needed to understand the association of transfusion-related mortality.

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