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Transfusion-related acute lung injury in obstetric hemorrhage: prevalence and risk factors.

Lesión pulmonar aguda inducida por transfusión en hemorragia obstétrica: prevalencia y factores de riesgo

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Abstract

OBJECTIVE: To determine the prevalence and risk factors of transfusion-associated lung injury in obstetric hemorrhage.

MATERIALS AND METHODS: Retrospective and comparative case series study, carried out in the Obstetric Intensive Care Unit (OICU) at the Hospital Materno Infantil ISSEMyM from 2014 to 2018. Patients with history of obstetric haemorrhage and transfusion were included. To associate the risk factors and the development of transfusion related acute long injury, χ^2, Fisher and Student's t tests were performed, considering a significant p value less than 0.05 and a CI95%.

RESULTS: From a total of 511 records, the prevalence of obstetric hemorrhage was 28.37%. The mean age was 32.57 years, with an average bleeding of 2679 mL. The prevalence of transfusion related acute long injury in the study was 11.03%. A significant association was found between massive transfusion and the development of transfusion related acute long injury (p = 0.001, OR: 21,167;95%CI: 3,507 - 127,747), in addition to the association of transfusion related acute long injury with any type of blood component: erythrocyte concentrate (p = 0.004), fresh frozen plasma (p = 0.0001), platelet apheresis (p = 0.015) and cryoprecipitates (p = 0.002).

CONCLUSIONS: There are very few documented reports of transfusion related acute long injury in pregnancy and puerperium with obstetric hemorrhage. In the present study, the prevalence of transfusion related acute long injury in patients with obstetric bleeding was 11.03%. and the main cause of obstetric hemorrhage was uterine atony (45.5%). Massive transfusion and the use of blood components had a significant association with the development of transfusion related acute long injury.

KEYWORDS: Transfusion-related acute lung injury, TRALI, Obstetric Hemorrhage.

Resumen

OBJETIVO: Determinar la prevalencia y factores de riesgo de lesión pulmonar asociada con transfusión en hemorragia obstétrica.

MATERIALES Y MÉTODOS: Estudio de serie de casos retrospectivo y comparativo llevado a cabo en la Unidad de Cuidados Intensivos Obstétricos del Hospital Materno Infantil ISSEMyM del 2014 al 2018. Se incluyeron expedientes de pacientes con hemorragia obstétrica y transfusión. Para asociar los factores de riesgo y la lesión pulmonar aguda relacionada con la transfusión (TRALI), se efectuaron pruebas de χ^2, Fisher y t de Student, se consideró significativo un valor de p menor a 0.05 e IC95%.

RESULTADOS: La prevalencia de hemorragia obstétrica en 511 expedientes fue 28.37%. La edad media de las pacientes 32.57 años, con sangrado promedio de 2679 mL. La prevalencia de lesión pulmonar aguda relacionada con la transfusión fue de 11.03%. Se encontró asociación significativa entre la transfusión masiva y la lesión pulmonar

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aguda relacionada con la transfusión (p = 0.001, OR de 21.167, IC95%: 3.507-127.747) y con lesión pulmonar aguda relacionada con la transfusión con cualquier tipo de hemocomponente: concentrado eritrocitario (p = 0.004), plasma fresco congelado (p = 0.0001), aféresis plaquetaria (p = 0.015) y crioprecipitados (p = 0.002).

CONCLUSIONES: Existen muy pocos reportes documentados de lesión pulmonar aguda relacionada con la transfusión en el embarazo y puerperio que hayan cursado con hemorragia obstétrica. En este estudio, la prevalencia de lesión pulmonar aguda relacionada con la transfusión, en pacientes con hemorragia obstétrica, fue del 11.03% y la principal causa de hemorragia obstétrica fue la atonía uterina (45.5%). La transfusión masiva y la aplicación de hemocomponentes tuvieron asociación significativa con la lesión pulmonar aguda relacionada con la transfusión.

PALABRAS CLAVE: Lesión pulmonar aguda inducida por transfusión; TRALI, hemorragia obstétrica.

BACKGROUND

Obstetric hemorrhage continues to be the leading cause of maternal morbidity and mortality worldwide. It occurs in 5% of all births and causes 140,000 deaths a year, which is equivalent to one death every 4 minutes.[1] In Mexico, it constitutes 16.7% of maternal mortality until week 38 of 2020.[2] The successful management of obstetric hemorrhage involves the execution of various tasks that include determining the etiology of the bleeding, administration of targeted and specific treatment of obstetric hemorrhage, and transfusion in case of clinical indication. When the percentage of loss is greater than 40%, the majority critically ill patients already have severity data that make them immediately candidates for the administration of blood products to avoid death.[3]

Massive transfusion, historically defined as the replacement by transfusion of 10 units of red cells in 24 hours, is a response to massive and uncontrolled hemorrhage. With more rapid and effective therapy, alternative definitions such as three units of red blood cells over one hour or any four blood components in 30 minutes are more sensitive in identifying patients needing rapid issue of blood products for serious injuries because of uncontrolled hemorrhage.[4,5]

This transfusion therapy carries, among others, the risk of adverse reactions, from mild to very serious that can even lead to death. In most cases blood transfusions are well tolerated; however, undesirable effects known as transfusion reactions occasionally occur.[6] Transfusion-related acute lung injury (TRALI) is a clinical syndrome that presents as acute hypoxemia and non-cardiogenic pulmonary edema during or after a transfusion of blood products.[7] Historical estimates suggest that TRALI occurs at a rate of 0.04 to 0.1% of transfused patients or 1 in 5,000 transfused blood products.[8]

The characteristic clinical presentation of TRALI is the sudden onset of hypoxemic respiratory failure during or shortly after transfusion of a blood product.[9] Symptoms can be delayed for up to six hours, but generally begin within an hour or two after starting the infusion of the blood component.[10] Most cases occur within a few minutes of starting a transfusion.[11]

There are few studies that associate TRALI with obstetric hemorrhage, so the present study focused on determining the prevalence and risk factors of TRALI in mexican patients who had obstetric hemorrhage and transfusion in Obstetric Intensive Care Unit (OICU) at the Hospital Materno Infantil ISSEMyM.

MATERIALS AND METHODS

Retrospective and comparative case series study. The records of patients who presented obstetric hemorrhage, who were transfused and admitted to the Obstetric Intensive Care Unit during the period from January 2014 to December 2018, at the ISSEMyM Maternal and Child Hospital were collected. Variables such as gestation number, pregnancy termination route, body mass index, placenta previa, uterine atony, placental accreta, massive transfusion, type of obstetric hemorrhage, and TRALI diagnosis were collected. The quantitative variables identified were volume of bleeding, hemoglobin, fibrinogen, INR and platelet count on admission to the ICU; as well as days of hospital stay, age and type of blood component transfused. For the diagnosis of TRALI, the following definition was used: acute onset accompanied by hypoxemia of PO_2 / FiO_2 < 300 mmHg or SaO_2 < 90% in room air, clear evidence of bilateral pulmonary edema in images, onset during or within 6 hours after transfusion and not temporally related to an alternative risk factor for ARDS (acute respiratory distress syndrome). The inclusion criteria were complete clinical records of patients with major obstetric hemorrhage who were admitted to the Intensive Care Unit and who received transfusion of any blood component. Study exclusion criteria: termination of pregnancy outside the institution and / or patients who required transfer to another institution.

Demographic and clinical data were collected and organized in a database using SPSS version 22 software for MAC (SPSS, Inc, Chicago, IL, USA). For the descriptive statistical analysis, quantitative variables were expressed as measures of central tendency, either means with standard deviation and 95% confidence intervals; In addition, they were represented in histogram-type graphs and frequency tables. For the qualitative values, it was documented as percentages and pie-type graphs. An analysis using the chi-square test, Fisher and Student's t test was used to associate a risk factor and the development of TRALI, considering the value of $p < 0.05$ with a 95% confidence interval (95%CI) to be significant.

RESULTS

From a total of 511 records registered in the intensive care unit during the period 2014 to 2018, it was calculated that the general prevalence of obstetric hemorrhage was 28.37%. (n = 145). Of these, 23.4% (n = 34) presented higher moderate obstetric hemorrhage and 76.6% (n = 111) higher severe obstetric hemorrhage. Based on the size of the population and the sample used, the reliability percentage of the study was 95%

The mean age of the sample was 32.57 ± 6.085 years, and the mean bleeding was 2.679 ± 1229.138 mL. The population was classified as a population with normal weight 15.2% (n = 22), overweight 42.1% (n = 61), obesity grade I 31.7% (n = 46), obesity grade 2 9.0% (n = 13) and morbid obesity 2.1% (n = 3) according to the body mass index.

Regarding demographic data, 9.7% (n = 14) were single women, 71.7% (n = 104) were married, 17.9% (n = 26) in common union and 0.7% (n = 1) were divorced. The delivery was by cesarean section in 65.5% (n = 95), vaginal delivery in 22.8% (n = 33), and abortion in 11.7% (n = 17). 23.4% (n = 34) were primigravida and 76.6% (n = 111) were multigravida. Considering the total population (n = 145); the most frequent causes

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of obstetric hemorrhage were uterine atony (n = 66, 45.5%), placental accreta (33.8%; n = 49,), placenta previa (21.4%; n = 31) and obstetric trauma (19.3%; n = 28) (**Figure 1**). The mean days of stay in the obstetric intensive care unit was 3.59 ± 2.66 days, with a maximum of 13 days and a minimum of 1 day.

In total, 1,208 blood components were transfused according to hemoglobin serum levels, INR, fibrinogen and platelets at ICU admission. The mean of this blood components were 9.148±1.974 mg/dL, 1.25 ± 0.764, 291.91 ± 124.29 mg/dL y 143 ± 72.28 mL, respectively, of which 536 units were erythrocyte concentrates (EC), 397 units fresh frozen plasmas, 34 units platelet apheresis, and 241 units cryoprecipitates. Transfusion-related acute lung injury had a prevalence of 11.03% (n = 16). Other adverse reactions to transfusion presented in the study sample were post-transfusion hemolysis (4.82%, n = 7), allergic reaction (1.37%, n = 2,) and fever (1.37%, n = 2). Massive transfusion was identified in 6 patients (4.13%). The development of TRALI was associated with the administration of massive transfusion (p = 0.001; OR = 21.167; 95% CI, 3.507 - 127.747).

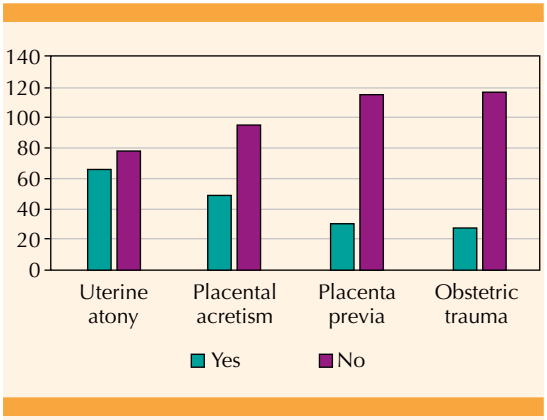

Figure 1. Obstetric hemorrhage causes in the study population.

A univariate analysis of the risk of developing TRALI and the transfused blood component was performed, observing positive significance for erythrocyte concentrates (p = 0.004, 95% CI 1.166 to 5.136), fresh frozen plasma (p = 0.0001, 95% CI 2.124 to 6.05), platelet apheresis (p = 0.015, 95% CI 0.135 to 1.055) and cryoprecipitates (p = 0.002, 95% CI 3.258 to 12.255). Likewise, hemoglobin, INR, fibrinogen, platelets and the days of stay in the obstetric intensive care unit (ICU), age and bleeding were analyzed (**Table 1**).

In the study group that presented TRALI (n = 16), 75% (n = 12) were multigravida and 93.75% (n = 15) had severe major obstetric bleeding vs the group that did not have TRALI (n = 129), 76.7% (n = 99) were multigravida and 74.4% (n = 96) had severe major obstetric bleeding. As obstetric complications in the TRALI group, 10 hysterectomies (62.5%) and 6 abdominal packings were performed versus 68 hysterectomies (52.7%) and 8 abdominal packings in patients without TRALI.

DISCUSSION

Obstetric hemorrhage is one of the leading causes of maternal death in Mexico and one of the main admissions to the obstetric intensive care unit (ICU). The prevalence of ICU admissions for obstetric hemorrhage in the present study was 32.6% and for severe major obstetric hemorrhage was 76.6%, in contrast to a study conducted at the Hospital General de Mexico with reported prevalences of 15% (n = 44, n = 287).[12]

In the United States, the leading cause of obstetric bleeding is uterine atony, which complicates approximately 1 in 40 births, corresponding to 80%.[13] In the present study, the main cause of OH was 45.5% uterine atony, followed by placental accreta (33.8%) and placenta previa (21.4%). In 1983, Popovsky and his colleagues described 5 cases of non-cardiogenic pulmonary

Table 1. Association of TRALI with blood components and quantitative variables

Variable Population N=145	TRALI n = 16 X ± SD	NO TRALI n = 129 X ± SD	P value	CI95%
ICU stay (days)	7.06 ± 3.64	3.16 ± 2.17	0.001	1.939 to 5.876
Age (years)	34.06 ± 5.07	32.39 ± 6.19	0.238	-1.193 to 4.542
Bleeding (mL)	3921.88 ± 1374.89	2525.27 ± 1123.03	0.001	643.868 to 2149.340
Hemoglobin (g/L)	8.558 ± 1.832	9.221 ± 1.985	0.205	-1.697 to 0.367
INR	1.419 ± 0.747	1.229 ± 0.766	0.350	-0.210 to 0.590
Fibrinogen (mg/dL)	240.38 ± 135.74	298.30 ± 121.84	0.078	-122.57 to 6.71
Platelets (mL)	99.06 ± 23.39	148.92 ± 74.41	0.008	-86.95 to -12.77
Erythrocyte concentrate (units)	6.50 ± 3.69	3.35 ± 1.85	0.004	1.166 to 5.136
Fresh frozen plasma (units)	6.38 ± 3.65	2.29 ± 1.80	0.0001	2.124 to 6.05
Platelet apheresis (units)	0.75 ± 0.86	0.17 ± 0.42	0.015	0.135 to 1.055
Cryoprecipitate (units)	8.56 ± 8.41	0.81 ± 2.43	0.002	3.258 to 12.255

TRALI: transfusion-related acute lung injury.

edema after transfusion of packed red blood cells (PRBC) or whole blood and gave the syndrome its current name, transfusion-related acute lung injury (TRALI).[14]

In 2019, a modified classification scheme was proposed based on new knowledge gained since the 2004 Canadian Consensus Conference. This classification reaffirmed that TRALI remains a clinical diagnosis and does not require the detection of related leukocyte antibodies (**Table 2**).[15]

The most widely accepted theory of the pathogenesis of TRALI is that it occurs by a

Table 2. New TRALI definitions as proposed in 2019

Category	Definition
TRALI type I	No risk factors for ARDS and all the following criteria are met: Acute onset Hypoxemia ($PaO_2/FiO2 \leq 300$ mmHg or $SpO_2 < 90\%$ on room air) Clear evidence of bilateral pulmonary edema on imaging No evidence of LAH or, if LAH is present, it is judged to not be the main contributor to the hypoxemia Onset during or within 6 hours of transfusion No temporal relationship to an alternative risk factor for ARDS
TRALI type II	Risk factors for ARDS are present (but ARDS has not been diagnosed) or mild ARDS at baseline but with respiratory status deterioration that is judged to be due to transfusion based on both of the following: Findings as described in categories a and b of TRALI type I Stable respiratory status in the 12 hours before transfusion

From: Vlaar APJ, Toy P, Fung M, et al.[15]
TRALI: transfusion-related acute lung injury; ARDS: acute respiratory distress syndrome; PaO_2/FiO_2: ratio of arterial oxygen tension to the fraction of inspired oxygen; SpO_2: peripheral arterial oxygen saturation as measured by pulse oximetry; LAH: left atrial hypertension.

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two-stroke mechanism: the first involves the sequestration and priming of neutrophils in the pulmonary microvasculature, and the second by the activation of receptor neutrophils by a factor in the blood product producing release of cytokines, oxygen reactive substances, oxidases and proteases that damage the pulmonary endothelium, causing inflammatory (hydrostatic) pulmonary edema.[16]

Previous hemovigilance monitoring studies suggest that between 6.7-15% of reported TRALIs occur in obstetric-gynecological patients,[17] but the statistical data are still confusing because many hospitals do not have the caution of epidemiological reporting of cases.[18]

On the other hand, a multidisciplinary working group that analyzed the TRALI cases extracted from the database of the French hemovigilance network (2007-2008) calculated an overall incidence of TRALI / pTRALI of 16.9%.[19] The present study agrees with these reports, since the prevalence of TRALI was identified as 11.03%.

The administration of the different blood components was associated with the development of TRALI, matching with previous reports[17]. TRALI has been associated with virtually all blood products, and high-volume plasma components have been consistently shown to carry the highest risk per component or per transfusion episode[15]. Massive transfusion increases the risk of complications, such as acute lung damage, acute kidney damage, hypersensitivity and fever.[20] In the present study, massive transfusion was positively associated with the development of TRALI ($p = 0.001$; OR = 21.167; 95%CI: 3.507-127.747).

There are very few documented reports of TRALI in patients with obstetric hemorrhage. It is vitally important to establish a timely diagnosis of TRALI to provide adequate treatment, since pregnant women are one of the most vulnerable populations due to all the adaptive pulmonary changes produced during pregnancy.

CONCLUSIONS

Transfusion-associated acute lung injury (TRALI) in the analyzed population was 11.03%. Massive transfusion and the use of blood components are associated with the development of TRALI ($p < 0.05$). The prevalence of obstetric hemorrhage in the obstetric intensive care unit was 32.6%. Uterine atony was the most important cause of obstetric hemorrhage (45.5%). 76.6% presented more severe OH (greater than 2000 mL).

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