

Universal definition of perioperative bleeding in cardiac surgery adults and association with mortality in a Mexican Cardiovascular Critical Care Unit

Definición universal de sangrado perioperatorio en cirugía cardiaca adultos y asociación con mortalidad en una Unidad de Terapia Intensiva Cardiovascular de México

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Abstract

Background: Bleeding as a complication is associated with poorer results in cardiac surgery. There is increasing evidence that the use of blood products is an independent factor of increased morbidity, mortality, and hospital costs. Dyke et al. established the universal definition of perioperative bleeding (UDPB). This classification is more precise defining mortality in relation to the degree of bleeding. **Methods:** A descriptive and analytical retrospective study of a database of patients underwent cardiac surgery from January 1, 2016, to December 31, 2017, was performed. The primary objective of the study was to look at mortality associated with the degree of bleeding using the UDPB. **Results:** A total of 918 patients who went to cardiac surgery were obtained. Most of the population was classified as insignificant bleeding class ($n = 666$, 72.9%), and for massive bleeding the lowest proportion ($n = 25$, 2.7%). For the primary outcome of 30-day mortality, a significant difference was found between the groups, observing that it increased to a higher degree of bleeding. This was corroborated by multivariate logistic regression analysis that was adjusted to EuroScore II and cardiopulmonary bypass (CPB) duration, finding an independent association of the bleeding class with 30-day mortality ($OR, 95\%, 5.82 [2.22-15.26], p = 0.0001$). **Conclusions:** We found that the higher the degree in UDPB was associated with higher mortality independently to EuroScore II and CPB duration for adult patients undergoing cardiac surgery.

Key words: Cardiac surgery. Bleeding. Blood transfusion.

Resumen

Antecedentes: El sangrado como complicación está asociado a peores resultados en cirugía cardiaca. Existe una evidencia cada vez mayor que la transfusión de productos sanguíneos por si solo es un factor independiente de incremento en la morbilidad, mortalidad, y costos hospitalarios. Dyke y colaboradores establecieron la definición universal de sangrado perioperatorio. Esta clasificación es más precisa en definir mortalidad en relación con el grado de sangrado. **Material y métodos:** Se

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realizo un estudio descriptivo y analítico de tipo retrospectivo de una base de datos de pacientes que fueron a cirugía cardiaca del 1 enero del 2016 al 31 de diciembre del 2017. El objetivo primario del estudio fue observar la mortalidad asociada con el grado de sangrado utilizando la definición universal de sangrado perioperatorio. **Resultados:** Se obtuvieron un total de 918 pacientes que fueron a cirugía cardiaca. La mayor parte de la población fue clasificada como clase de sangrado insignificante ($n = 666$, 72.9%), y para sangrado masivo la menor proporción ($n = 25$, 2.7%). En el desenlace primario de mortalidad a 30 días se encontró una diferencia significativa entre los grupos, observando que aumentada a mayor clase de sangrado. Esto fue corroborado mediante un análisis multivariado regresión logística que fue ajustado a con EuroScore II y el tiempo de bomba de circulación extracorpórea, encontrando una asociación independiente de la clase de sangrado con mortalidad a 30 días ($OR, 95\%, 5.82 [2.22-15.26], p = 0.0001$). **Conclusiones:** Encontramos que cuanto mayor era el grado en la UDPB se asociaba con una mayor mortalidad independientemente de EuroScore II y la duración del bypass cardiopulmonar para pacientes adultos sometidos a cirugía cardíaca.

Palabras clave: Cirugía cardíaca. Sangrado. Transfusión de sangre.

Introduction

Bleeding is an important issue in cardiac surgery, about 20% of all blood products are transfused in this scenario around the world¹. Bleeding as a complication is associated with poorer results in cardiac surgery. In a retrospective analysis that included 1188 cardiac surgery patients, the presence of excessive post-operative bleeding was associated with an increase incidence of surgical re-exploration ($OR = 103.7$, 95% CI = 45.6-235.4, $p < 0.0001$), post-operative stroke ($OR = 3.3$, 95% CI = 1.6-7.0, $p = 0.003$), mechanical ventilation for more than 24 h ($OR = 3.4$, 95% CI = 1.8-6.4, $p = 0.0002$), stay in the intensive care unit (ICU) for more than 72 h ($OR = 1.4$, 95% CI = 1.2-3.2, $p < 0.0001$), and increase mortality ($OR = 2.9$, 95% CI = 2.9-3.0, $p < 0.001$)². Therefore, excessive post-operative bleeding is associated with an increase in hospital costs³.

In addition, there is growing evidence that the transfusion of blood products is an independent factor of increase morbidity, mortality, and hospital costs^{4,5}.

Post-operative bleeding has been established as an important outcome measure in clinical practice and clinical trials. Despite having precise definitions for other complications in cardiac surgery, there is no standardized definition for post-operative bleeding, making difficult to interpret clinical trials and evaluate the management of blood products. We propose the implementation of the universal definition of perioperative bleeding (UDPB) in adult cardiac surgery to standardize nomenclature, improve outcome definitions, and be useful in future clinical trials.

Materials and methods

We conducted a retrospective descriptive and analytical study of one hospital. The data were obtained

from a database of the cardiovascular ICU of the National Institute of Cardiology Ignacio Chavez in Mexico City. All adult patients ≥ 18 years old who underwent cardiac surgery from January 1, 2016, to December 31, 2017, were included in the study. Congenital cardiac surgery patients were excluded from the study. The information included in the database was supplemented with information obtained from the files if necessary. The primary objective of the study was to look at mortality associated with the degree of bleeding according to the classification of the UDPB (Table 1). Secondary objectives were to determine whether a greater degree of bleeding was related to an increase stay in the ICU, an increase in hospital stay, and increase events of stroke and acute kidney injury (AKI). The study was approved by the local ethics committee with a waiver of written informed consent.

Statistical analysis

Continuous variables were represented with medians (interquartile ranges) and for categorical variables number (n) and percentages (%) were shown. Subsequently, patients were divided into five different groups according to the degree of bleeding using the UDPB. For comparisons of continuous variables Mann-Whitney U-test was used, and Fisher exact test for categorical variables. For those variables with statistical significance (α value ≤ 0.1) a multivariate logistic regression analysis was made, to determine if the degree of bleeding is independently associated with 30-day mortality. Crude mortality by class of bleeding was adjusted to cardiopulmonary bypass (CPB) duration and EuroScore II, which were the variables that were found with significance in the multimodal regression analysis.

Table 1. Universal definition for perioperative bleeding in adult cardiac surgery

Bleeding categories according to the UDPB in adult cardiac surgery									
Bleeding definition	Sternal closure delayed	Post-operative chest tube blood loss within 12 h (mL)	PRBC (units)	FFC (units)	PLT (units)	Cryoprecipitate	PCCs	rFVIIa	Re-exploration/tamponade
Class 0 (Insignificant)	No	< 600	0	0	0	No	No	No	No
Class 1 (Mild)	No	601-800	1	0	0	No	No	No	No
Class 2 (Moderate)	No	801-1000	2-4	2-4	Yes	Yes	Yes	Yes	Yes
Class 3 (Severe)	Yes	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes
Class 4 (Massive)	N/A	> 2000	> 10	> 10	N/A	N/A	N/A	Yes	N/A

UDPB: universal definition for perioperative bleeding; PRBC: packed red blood cells; FFP: fresh frozen plasma; PLT: platelet concentrates; PCCs: prothrombin complex concentrates; rFVIIa: recombinant activated factor VII; N/A: not applicable. The number of PRBCs used should only be considered in the UDPB when accompanied by other signs of perioperative bleeding. If different categories indicate mixed definitions of bleeding, the worst definition applies.

Results

A total of 918 patients were obtained. The median age was 59 years, with a proportion of women of 42%. About 21.4% of patients previously used platelet anti-aggregant. The highest percentage of surgeries performed in our hospital was valvular type (69.9%). About 32% of the surgeries were an emergency intervention. The overall mortality was 8.1%. Complications for stroke were found in 1% and AKI in 7.8% of the patients. Most of the population was classified as insignificant bleeding class ($n = 666$, 72.9%), and for massive bleeding the lowest proportion ($n = 25$, 2.7%) (Table 2).

In the comparison by groups defined by the class of bleeding, significant differences were found between the CPB and EuroScore II, both being higher in Class 4 compared to the rest. A significant difference was observed in the number of events of stroke and AKI, being more frequent in Class 4 (Table 3).

In the primary outcome of 30-day mortality, a significant difference was found between the groups, observing that it increased to a higher class of bleeding. This was corroborated by a multivariate logistic regression analysis that was adjusted to EuroScore II and CPB duration, finding an independent association of the bleeding with 30-day mortality (OR, 95%, 5.82 [2.22-15.26], $p = 0.0001$) (Table 4). Subsequently, an adjustment of the mortality by groups was made, which is shown in figure 1.

Discussion

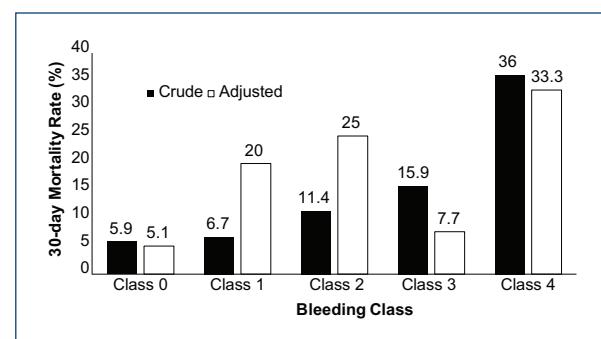
Excessive bleeding after cardiac surgery is a complex clinical problem despite significant advances in surgical techniques, anesthetic management, and critical care. It is generally accepted is better to avoid the use of blood products as much as possible; however, all cardiac surgery patients are at risk of bleeding and it remains unclear the threshold when the bleeding becomes clinically significant. The way to answer these questions is through the consensus and application of a more precise definition of bleeding.

Mehran et al. published a consensus to define bleeding and be used in cardiovascular clinical trials, but applicable in the context of acute coronary syndromes⁶. In cardiac surgery, the first studies measure bleeding through post-operative chest tube output, mainly in decision-making to emergency reoperation⁷⁻⁹. On the other hand, other studies quantified the degree of bleeding by the number of globular packages transfused^{10,11}. However, the transfusion strategy of each center may vary, including the hemoglobin threshold, which a globular package is indicated¹². Ranucci et al. in a retrospective study of a single center with 16,154 patients defined major bleeding by quantifying the chest tube output and it was associated with higher mortality with a 12% increase of relative risk of death for each 100 ml of increment in the first 12 h of postoperative bleeding¹³. Taking this as a basis, Dyke et al. established the concept of UDPB, ranking 5 degrees of bleeding

Table 2. Patient characteristics

Patient characteristics	
Total patients	918
Demographics	
Age (years)	59 [50-67]
Sex female	384 (42)
BMI	26.7 [23.6-28.8]
Comorbidity	
High Blood Pressure	387 (42)
Diabetes mellitus type 2	205 (22)
Chronic renal failure	23 (2.5)
Left ventricular ejection fraction < 50%	156 (17)
Preoperative therapy	
Aspirin	155 (16.9)
Clopidogrel	41 (4.5)
Warfarin	39 (4.2)
Pre-operative labs	
Hemoglobin, mg/dL	11.7 [10.2-13.1]
Creatinine, mg/dL	0.9 [0.79-1.10]
Type of surgery	
Coronary artery bypass graft	162 (17.6)
Valvular	642 (69.9)
Coronary artery bypass graft + Valvular	78 (8.5)
Aorta	36 (3.9)
Operation details	
Elective surgery	624 (68)
Emergency surgery	294 (32)
EuroScore II, %	2 [1.2-4.6]
CPB time, min	120 [97-161]
Class of bleeding	
Class 0 (Insignificant)	666 (72.9)
Class 1 (Mild)	75 (8.2)
Class 2 (Moderate)	70 (7.6)
Class 3 (Severe)	82 (8.9)
Class 4 (Massive)	25 (2.7)
Outcomes	
30-day mortality	74 (8.1)
Stroke	9 (1)
AKI	72 (7.8)
ICU length of stay, days	4 [2-5]
Hospital length of stay, days	23 [13-35]

BMI: body mass index; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; AKI: acute kidney injury; ICU: intensive care unit. Data presented as median [interquartile range] for continuous variables and counts (percentages) for categorical variables.

**Figure 1.** Mortality according to the universal definition for perioperative bleeding classification. Adjusted to EuroScore II and cardiopulmonary bypass duration.

considering the chest tube output, delayed sternal closure, the need for surgical re-exploration, and the use of blood products. This classification proposal is more precise in defining mortality in relation to the degree of bleeding¹⁴. More recently Colson et al. in a prospective multicenter study define active bleeding as blood loss > 1.5 ml/kg/h for 6 consecutive h in the first 24 h post-operatively, determining that this definition may be more appropriate for clinical decision-making¹⁵.

We used the classification proposed by Dyke in our hospital and observed an increase in mortality depending on the degree of bleeding. In the adjustment of mortality with other confounding variables (EuroScore II and CPB duration), the same result was also observed; however, for Classes 1 and 2 the adjusted mortality increases significantly, which can be related to the fact that those two groups have a lower EuroScore II and a lower CPB duration compared to the other groups. The results of our study are like the work of Dyke.

The limitations of this classification and our study are that it does not predict or identify risk factors for bleeding; it does not suggest any treatment or intervention, only attempts to define the degree of perioperative bleeding. We do not compare the UDPB with other classifications suggested in the literature to compare which one is superior to predict worse outcomes or mortality. Another limitation is the retrospective character of the study and only concludes association.

We strongly think the UDPB can be used in cardiac surgery to standardize nomenclature, improve outcome definitions, be useful in future clinical trials, and as a quality measure of care to manage and minimize transfusion.

Table 3. Outcome in patients for bleeding class

	Outcome in patients for bleeding class					
	Class 0	Class 1	Class 2	Class 3	Class 4	p value
CRF	17 (2.6)	1 (1.3)	3 (4.3)	2 (2.4)	0	0.74
LVEF < 50%	113 (17)	9 (12)	14 (20)	17 (20.7)	3 (12)	0.55
Aspirin	116 (17.4)	11 (14.7)	11 (15.7)	14 (17.1)	3 (12)	0.92
Clopidogrel	29 (4.4)	3 (4)	4 (5.7)	5 (6.1)	0	0.73
Warfarin	28 (4.2)	1 (1.3)	4 (5.7)	4 (4.9)	2 (8)	0.57
Creatinine, mg/dL	0.8 [0.7-1.2]	0.9 [0.8-1.1]	0.9 [0.7-1.3]	1 [0.8-1.1]	0.9 [0.7-1.2]	0.92
Hemoglobin, mg/dL	10.2 [9.7-11.9]	10.1 [8.6-12.1]	10.3 [9-13.6]	11.8 [10-13.6]	12.1 [9-14.6]	0.45
EuroScore II, %	2.3 [1.5-6-8]	1.8 [1.1-3.3]	2 [1.2-3.4]	2 [1.3-6.9]	4 [1.8-8.3]	0.003
CPB time, min	120 [100-140]	114 [103-150]	117 [93-163]	124 [97-152]	165 [105-223]	0.0001
Emergency surgery	205 (30.7)	21 (28)	24 (34)	34 (41.4)	10 (40)	0.26
Stroke	5 (0.8)	0	0	3 (3.7)	1 (4)	0.03
AKI	44 (6.6)	6 (8)	9 (12.9)	8 (9.8)	5 (20)	0.05
UCI LOS, days	6 [3-8]	4 [2-6]	5 [3-6]	5 [3-11]	4 [2-11]	0.02
HLOS, days	30 [23-35]	23 [15-29]	29 [16-36]	31 [15-44]	28 [18-36]	0.006
30-day Mortality	39 (5.9)	5 (6.7)	8 (11.4)	13 (15.9)	9 (36)	0.0001

CRF: chronic renal failure; LVEF: left ventricular ejection fraction; CPB: cardiopulmonary bypass; AKI: acute kidney injury; ICU LOS: intensive care unit length of stay; HLOS: hospital length of stay. Data presented as median [interquartile range] for continuous variables and counts (percentages) for categorical variables.

Table 4. Multivariate regression analysis for 30-day mortality

	OR (95% IC)	p value
Bleeding class*	5.82 (2.22-15.26)	0.0001

*Adjusted for EuroScore II and cardiopulmonary bypass duration.

More multicenter studies are needed to validate this classification and even establish it as a quality parameter in patient care in cardiac surgery.

Conclusions

Most cardiac surgical patients have post-operative bleeding without a clinical consequence. But for those with severe to massive bleeding, it can be catastrophic. We found that the higher the degree in UDPB was associated with higher mortality independently in our hospital population. We propose to use the UDPB for improving bleeding management and minimize transfusion in cardiac surgery patients; it can also serve as a measure for institutional quality improvement.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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